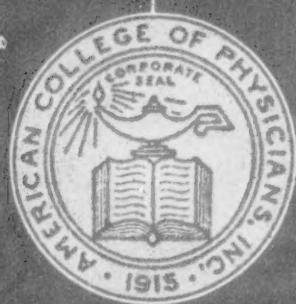


ANNALS

OF

INTERNAL MEDICINE



PUBLISHED MONTHLY BY
THE AMERICAN COLLEGE OF PHYSICIANS
VOLUME 55 • NUMBER 5

NOVEMBER 1961

**PROTECTION
IN ITS
SIMPLEST
FORM**

ESTOMUL™

IN ULCER THERAPY



**ONE MEDICATION RELIEVES PAIN, INHIBITS EROSION,
PROMOTES HEALING. UNIQUE IN SIMPLICITY,
COMPLETENESS OF ACTION AND CONVENIENCE**

Only ONE prescription to write

INDICATIONS:

Peptic Ulcer:
Duodenal Marginal
Gastric Esophageal
Hyperacidity and dyspepsia
Heartburn
Gastritis
Alcoholic gastritis
Gastroesophageal reflux
Esophagitis (without stricture)
Irritable bowel syndrome
Congenital shortening of esophagus
Chalasia of esophagus
Hiatus hernia of esophagus
Cardiospasm
Functional pylorospasm

DOSAGE:

Liquid and Tablets:
1 or 2 tablespoons or 1 or 2 tablets three times daily depending on severity of involvement.

SIDE ACTIONS:

Doses in excess of 6 tablets or 6 tablespoons daily may produce minor side actions such as dryness of the mouth or blurring of vision.

CONTRAINDICATIONS:

ESTOMUL should not be used in patients with organic pyloric obstruction or achalasia of esophagus. Use with caution in patients with renal impairment or insufficiency. Relative contraindications for anti-cholinergic drugs are glaucoma and prostatic hypertrophy which may lead to urinary bladder obstruction.

AVAILABILITY:

Tablets — Bottles of 100.

Liquid — Bottle of 12 fluid oz.

CAUTION: Federal law prohibits dispensing without prescription.

RESULTS

- RELIEVES SPASM AND REDUCES MOTILITY
- RETARDS ACID PRODUCTION
- PROMPT REDUCTION OF PAIN
- RAPID AND PROLONGED NEUTRALIZATION OF GASTRIC HYDROCHLORIC ACID TO DESIRABLE pH LEVEL
- COATS AND PROTECTS GASTRIC MUCOSA
- INHIBITS EROSION OF MUCOSA

ACTIONS

- ANTIACHOLINERGIC
orphenadrine hydrochloride
ANTISPASMODIC
- ANTISECRETORY
- TOPICAL ANESTHETIC
orphenadrine hydrochloride
- ANTACID
aluminum hydroxide-magnesium carbonate co-precipitate
- DEMULCENT
bismuth aluminate
- ANTIPEPTIC
bismuth aluminate

FORMULATION

Each ESTOMUL TABLET contains:
orphenadrine HCl 25 mg.
[2-dimethylaminomethyl (2-methylbenzhydryl) ether HCl]
bismuth aluminate 25 mg.
magnesium oxide 45 mg.
aluminum hydroxide-magnesium carbonate } co-precipitate 500 mg.

Each tablespoon (15 cc) ESTOMUL LIQUID contains:

orphenadrine HCl	25 mg.
[2-dimethylaminomethyl (2-methylbenzhydryl) ether HCl]	
bismuth aluminate	50 mg.
aluminum hydroxide-magnesium carbonate	315 mg.

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The obese patient may have two problems—overweight and depression. The more weight she puts on, the more she becomes depressed. The more depressed she becomes, the more she eats and puts on weight. It's a vicious cycle.

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Desbutal Gradumet accomplishes this by combining *two drugs in one* unique vehicle. Desoxyn® curbs the appetite and elevates the mood while at the same time Nembutal® counteracts any excessive stimulation. One prescription for Desbutal Gradumet treats both the obesity and the depression.

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receiving the right amount of medication to help maintain diet and emotional control. No forgotten doses. No midafternoon letdown. No change of drug effect. Just a steady release all day to decrease her appetite and improve her mood.

For complete indications, precautions, dosage, etc., send for the official literature. Your Abbott man has samples of both Desbutal 10 (10 mg. Desoxyn and 60 mg. Nembutal) and Desbutal 15 (15 mg. Desoxyn and 90 mg. Nembutal). Check with him. The new Gradumet form is the answer for the obese patient who is both overweight and depressed.

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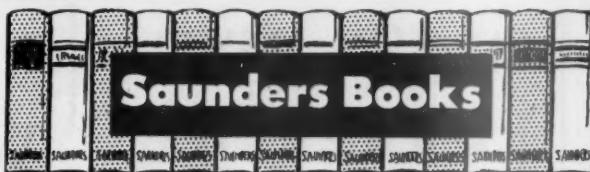
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3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956.
4. Eisfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

1 tablet all day



1 tablet all night

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Rich attention is paid to symptoms, physical signs, treatment and prognosis. Of valuable help in the clinical area is the chapter on bedside diagnosis of cardiac arrhythmias and conduction defects. This chapter offers simple but practical

points in the differential diagnosis of each arrhythmia. Another helpful section explains the role of emotions in producing disorders of cardiac rate.

In the wealth of timely material discussed you'll find: how electrolyte disturbances cause arrhythmias—a detailed discussion of the treatment of digitalis toxicity with potassium and other anti-arrhythmic agents—the use of vasoconstrictor drugs such as noradrenalin, methoxamine, vasoxyl and metaraminol for the treatment of various cardiac arrhythmias and conduction defects.

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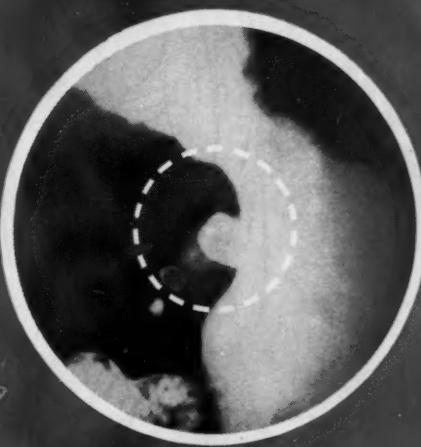
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[†]Russek, H.I.: Am J. Cardiol. 3:547 (April) 1959.

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References: W. J. Kolff, "Acute Renal Failure: Causes and Treatment," The Medical Clinics of North America, 39:1052 (July 1955). Peter Forsham, "Symposium on Adrenal Corticoid Therapy," Metabolism, 7:19 (Jan. 1958).



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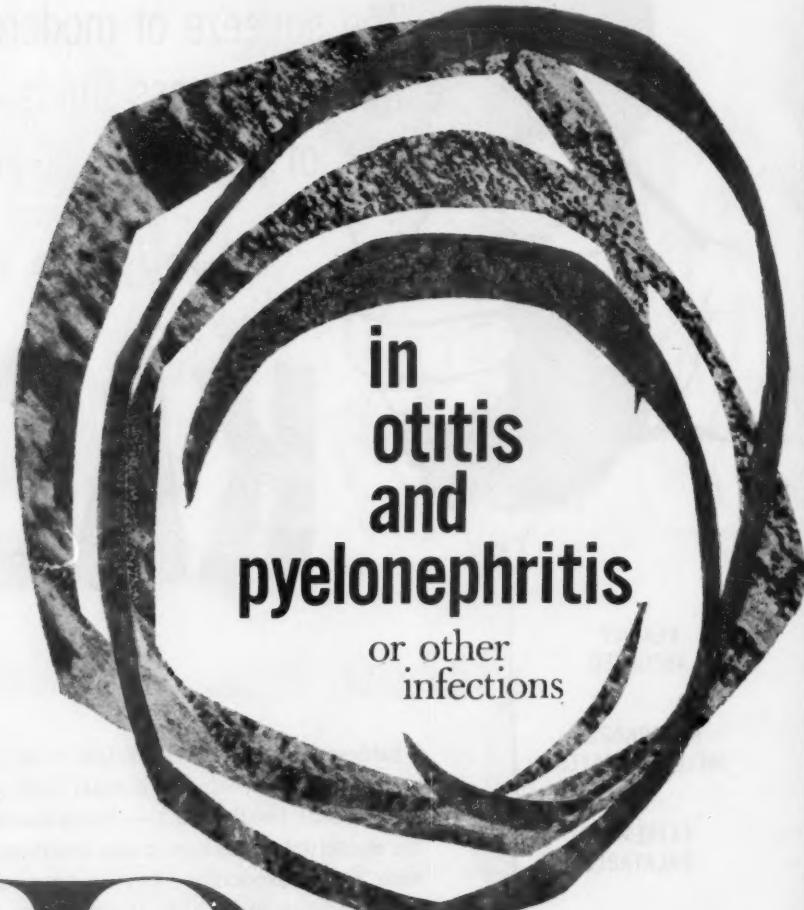
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CAPSULES, 150 mg., 75 mg. *Dosage:* Average infections—150 mg. four times daily. Severe infections—Initial dose of 300 mg., then 150 mg. every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. *Dosage:* 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into four doses.

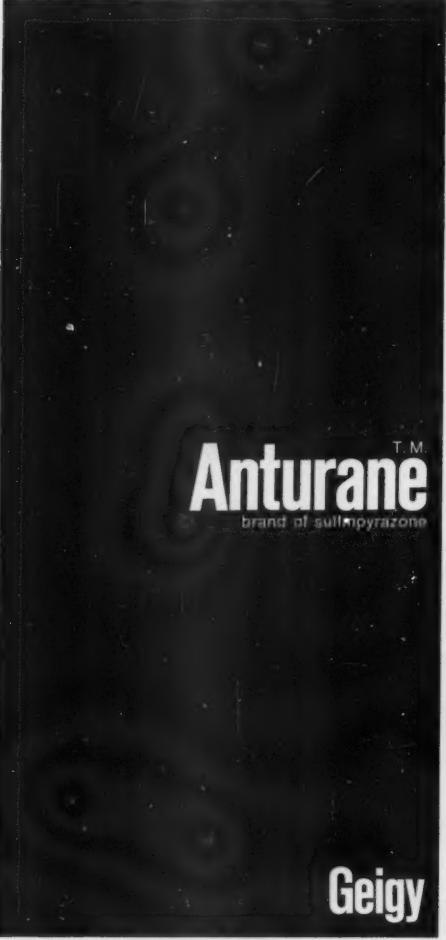
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References: 1. Seegmiller, J. E., and Grayzel, A. I.: J.A.M.A. 173:1078, 1965. 2. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. 1:332, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. 17:326, 1958. 4. Gutman, A. B., and Yü, T. F.: Bull. New York Acad. Med. 34:287, 1958.

Full product information regarding dosage, side effects, precautions and contraindications available on request.

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without serious side effects

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Capla acts centrally at the brainstem vasomotor center

Reduces blood pressure by central action;
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New therapy for hypertension

Because of its action at the brainstem vasomotor control center, Capla is a new therapy for hypertension. It is effective alone in the treatment of mild to moderate hypertension, and can be combined with diuretics or peripherally acting anti-hypertensives in more severe cases.

Exceptionally well tolerated

Capla acts rapidly, producing substantial blood pressure reduction within two hours, yet it does not produce postural hypotension. It has proved exceptionally well tolerated in clinical use and has no known contraindications. Capla has not produced changes in renal, hematological, hepatic or endocrine function. It is rapidly eliminated and has no cumulative effects.

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Controls blood pressure without serious side effects

Capla does not produce depression, postural hypotension, nasal congestion or gastric hyperacidity

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With Capla you have effective therapy without the unpleasant side effects which often cause patients to abandon treatment.

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Patients on Capla often report a mild calming effect. This effect, together with the unusual freedom from serious side effects, makes therapy gratifying for both the patient and the physician.

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Hypertensive patients with other disorders can receive Capla along with other medications.

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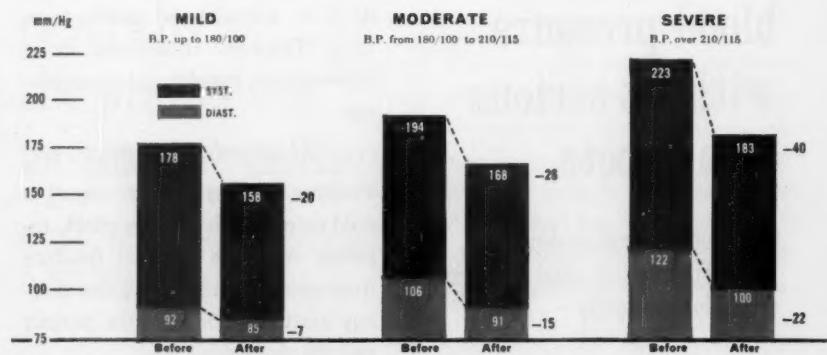
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CLINICAL & PHARMACOLOGICAL REPORTS

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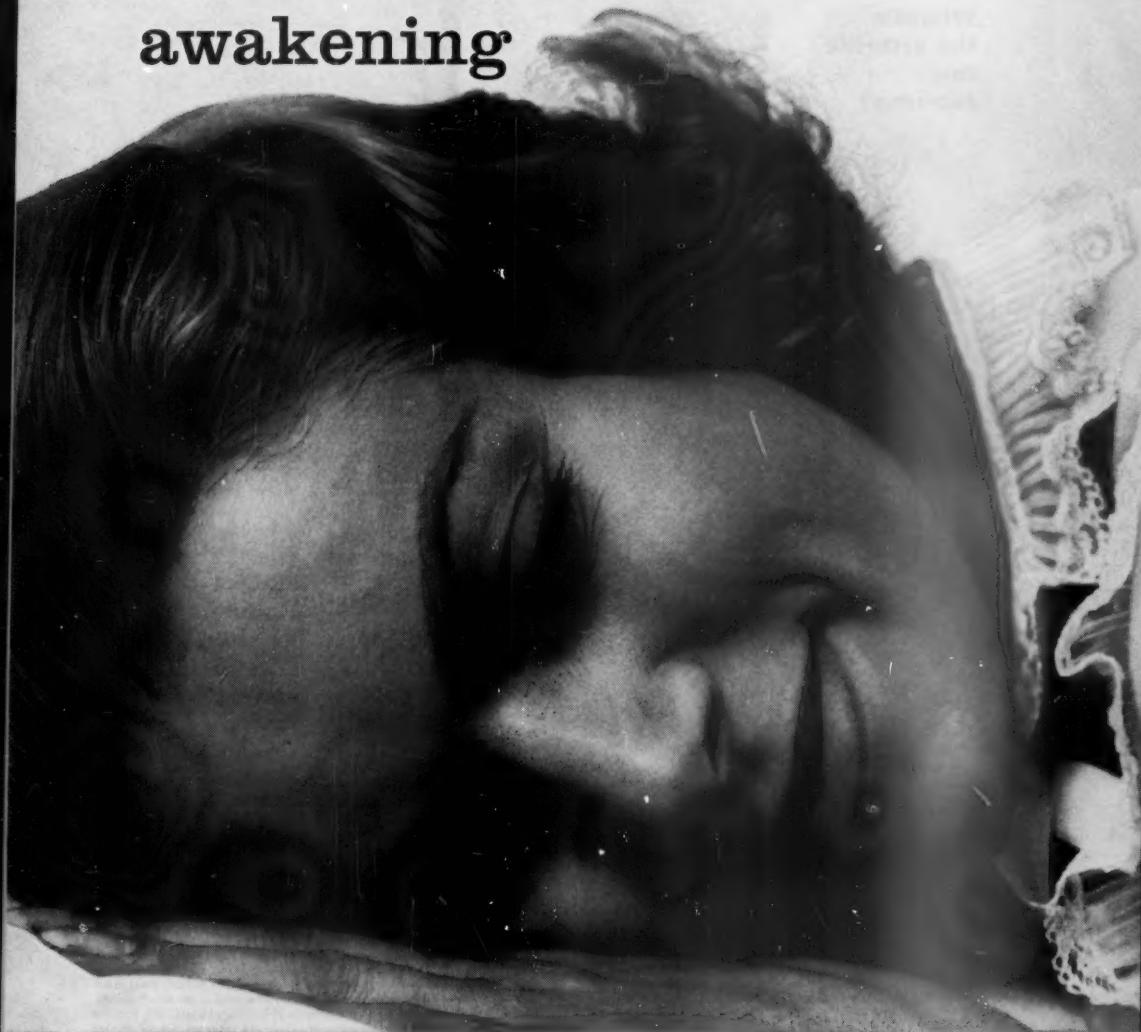
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**Thanks to
Medrol
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and he's
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The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

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	<i>Initial</i>	<i>Maintenance</i>
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Moderately severe	8 to 10 mg.	4 to 8 mg.
Moderate	6 to 8 mg.	2 to 6 mg.
Children	6 to 10 mg.	2 to 8 mg.

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Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, anti-rheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

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As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

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mean smoother steroid
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Supplied in bottles of 30 and 100.

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prescribe in one tablet the
bactericide without mutation
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that gives rapid pain relief
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Full dosage information, available upon request, should be consulted before initiating therapy.

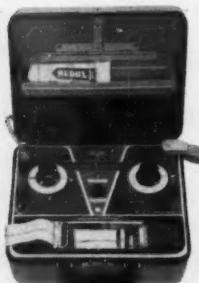


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Pleasant taste *plus* predictable, prompt response in diarrhea

Parepectolin combines paregoric, pectin, kaolin in a balanced, stable colloidal suspension, with a smooth, creamy consistency and a pleasant, mildly aromatic flavor. Parepectolin is compatible with antibiotics, and retains its uniform consistency and its good flavor.

Parepectolin: each fluid ounce—Paregoric (equivalent) 1.0 dram. Pectin 2.5 gr. Kaolin (specially purified) 85 gr Bottles of 4 and 8 fluid ounces.



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IN AGITATION AND APPREHENSION...



Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization,
relieves agitation, apprehension, anxiety

and "screens out"
certain side effects
of tranquilizers,
making it
virtually free of:

EXCESSIVE SEDATION
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"The side-effects which we have observed during trials with Mellaril have not been of a serious nature and we believe that the claim can justly be made that Mellaril has fewer side-effects than any other of the phenothiazine compounds."¹

In Agitation, Anxiety and Tension "The literature is replete with references to the phenothiazines and the role they play in the treatment of tension states, anxiety, and agitation. While numerous compounds have been introduced, the search continues for an ataractic that is not only effective, but is relatively free of annoying side effects. My experience with thioridazine [Mellaril] in 87 patients confirms the findings of other investigators regarding its efficacy in the control and treatment of various nervous and mental disturbances seen in everyday practice. Also, it does not induce parkinsonism, blood dyscrasia or liver damage."²

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients — 10 or 25 mg. t.i.d.; Psychotic patients — 100 mg. t.i.d.

Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

1. Sandison, R. A., Whitelaw, E., and Currie, J. D. C.: Clinical trials with Mellaril in the treatment of schizophrenia, Journal of Mental Science (British Journal of Psychiatry) 106:732, April, 1960. 2. Freed, S. C.: Thioridazine, a neuroleptic in general practice, International Record of Medicine, 172:644, Oct. 1959.





To our Readers, Subscribers, Contributors and Advertisers,

GREETINGS!

As we stand on the threshold of a New Year, it is good to pause to extend our Greetings to those intimately concerned with this Journal, those whose contact with us make it possible to present an even finer publication with each passing year.

May your Christmas be a very happy one and may your New Year bring you a full measure of health, inspiration and prosperity.

ANNALS OF INTERNAL MEDICINE





When the rhythm is wrong...PRONESTYL[®] HYDROCHLORIDE

Pronestyl[®] Hydrochloride (disopyramide) is indicated for the treatment of symptomatic atrial fibrillation. Pronestyl will be [a] effective in converting acute episodes of atrial fibrillation to normal sinus rhythm. The duration of action of Pronestyl has been shown to be longer than over 12 hours. This is because effects develop more rapidly than with quinidine. If a patient has not responded to one dose of Pronestyl, a second dose may be used. The most prolonged action of Pronestyl can be achieved by giving it at the end of a stimulation such as proctosigmoidoscopy.

Indication for conversion and maintenance of atrial fibrillation. Disopyramide is contraindicated in patients with known or suspected bradycardia, sinus bradycardia, sinus arrest, and second- or third-degree atrioventricular block. It may cause tachycardia, hypertension, hypotension, and peripheral edema. Product information available from Eli Lilly and Company.

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REFERENCES: 1. Kinsey, D.; Sise, H. S., and Whitelaw, G. P.: *Geriatrics* 16:397, 1961. 2. Gill, R. J., et al.: *Am. Pract. & Digest Treat.* 11:1007, 1960. 3. Smirk, F. H.: *Clin. Pharmacol. Ther.* 2:110, 1960. 4. Cohen, B. M.: *Curr. Ther. Res.* 3:160, 1961. 5. Cohen, B. M.: Paper presented at Indiana Acad. G.P., March, 1959. 6. Kirkendall, W. J.: *J. Iowa M. Soc.* 47:300, 1957. 7. Cherry, W. E., et al.: *Obst. & Gynec.* 9:515, 1957. 8. Reber, F. A.: *Illinoian M. J.* 108:171, 1955. 9. McCall, M. L., et al.: *Obst. & Gynec.* 6:297, 1953. 10. Finnerty, F. A.: *Am. J. Med.* 17:629, 1954. 11. Freis, E. D.: *South. M. J.* 51:1281, 1958. 12. Records of 41,851 cases, Medical Files, Irwin, Neisler & Co. 7/12/61. 13. Cohen, B. M.: *M. Times* 88:855, 1960. 14. Cohen, B. M.: Paper presented at the First Bahama Conference on Hypertension, January, 1961. 15. Cohen, B. M.: *Monographs on Therapy* 5:4, 1960.

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1. Dimitroff, S. P. et al.: Ann. Int. Med. 39:1189, 1953. 2. Pastor, B. H.: GP 22:85, 1960.

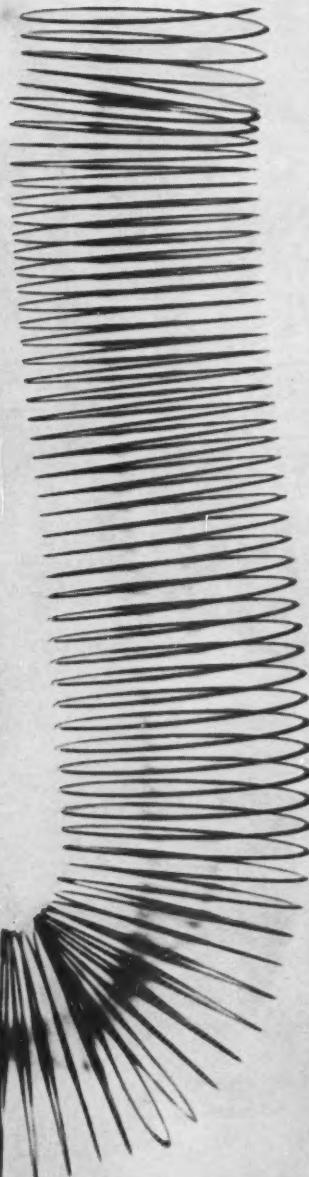
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However, in the diabetic patient, proteinuria also may be indicative of disorders unrelated to the diabetic state. *Postrenal* disturbances such as lithiasis, cystitis, pyelitis, bilharziasis or prostatic impairment may produce protein in the urine. *Renal* proteinuria may be due to predisposing factors such as abscess, carbuncle or gangrene. These are usually of a transitory nature. When diabetes is the only apparent contributing factor to the presence of persistent proteinuria ("diabetic proteinuria"), renal damage associated with degenerative diabetic nephropathy is usually indicated.*

*Nagy El Mahallawy, M., and Sabour, M. S.: J.A.M.A. 173:1783 (Aug. 20) 1960.

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From the beginning, woman has been a vassal to the temporal demands—and frequently the aberrations—of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement, or suspension of cyclic function and procreative potential. This new physiologic control is symbolized in an illustration borrowed from ancient Greek mythology—Andromeda freed from her chains.

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THE BASIC ACTION

ENOVID closely mimics the balanced progestational-estrogenic action of the functioning corpus luteum. This action is readily understood by a simple comparison. In effect, ENOVID induces a physiologic state which simulates early pregnancy—except that there is no placenta or fetus. Thus, as in pregnancy, the production or release of pituitary gonadotropin is inhibited and ovulation suspended; a pseudodecidual endometrium ("pseudo" because neither placenta nor fetus is present) is induced and maintained.

Further, during ENOVID therapy, certain symptoms typical of normal pregnancy may be noted in some patients, such as nausea—which is usually mild and disappears spontaneously within a few days—breast engorgement, some degree of fluid retention, and often a marked sense of well-being. There is no androgenicity. ENOVID is as safe as the normal state of pregnancy.

THE BASIC APPLICATIONS

1. Correction of menstrual dysfunction. Emergency treatment of severe dysfunctional uterine bleeding is promptly effective following the administration of ENOVID in larger doses. Cyclic therapy with ENOVID controls less severe dysfunctional uterine bleeding. In amenorrhea cyclic therapy with ENOVID establishes a pseudodecidual endometrium providing the patient has endometrial tissue capable of response.

2. Ovulation suppression (to suspend fertility). For this purpose ENOVID is administered cyclically, beginning on day 5 through day 24 (20 daily doses). The ovary remains in a state of physiologic rest and there is no impairment of subsequent fertility. When ENOVID is prescribed for this cyclic use over prolonged periods, a total

of twenty-four months should not be exceeded until continuing studies indicate that its present lack of undesired actions continues for even longer intervals. Such studies are now in their seventh year and will regularly be reviewed for extension of the present recommendation.

3. Adjustment of the menses for reasons of health (impending hospitalization for surgery, during treatment of Bartholin's gland cysts, acute urethritis, rectal abscess, trichomonial or monilial vaginitis), or other special circumstances considered valid in the opinion of the physician. For this purpose ENOVID may be started at any time in the cycle up to one week before expected menstruation. Upon discontinuation, normal cyclic bleeding occurs in three to five days.

4. Endometriosis. Continuous therapy with ENOVID corrects endometriosis by producing a pseudodecidual reaction with subsequent absorption of aberrant endometrial tissue.

5. Threatened and habitual abortion. ENOVID should be used as emergency treatment in threatened abortion although symptoms may occur too late to be reversible. Continuous therapy with ENOVID in habitual abortion is based on the physiology of pregnancy. ENOVID provides balanced hormone support of the endometrium, permitting continuation of pregnancy when endogenous support is otherwise inadequate.

6. Endocrine infertility. ENOVID has been used successfully in cyclic therapy of endocrine infertility, promoting subsequent pregnancy through a probable "rebound" phenomenon.

THE BASIC DOSAGE

Basic dosage of ENOVID is 5 mg. daily in cyclic therapy, beginning on day 5 through day 24 (20 daily doses). Higher doses may be used with complete safety to prevent or control occasional "spotting" or breakthrough bleeding during ENOVID therapy, or for rapid effect in the emergency treatment of dysfunctional uterine bleeding and threatened abortion.

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Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:
Pectin	142.8 mg.	hyoscyamine sulfate 0.1037 mg.
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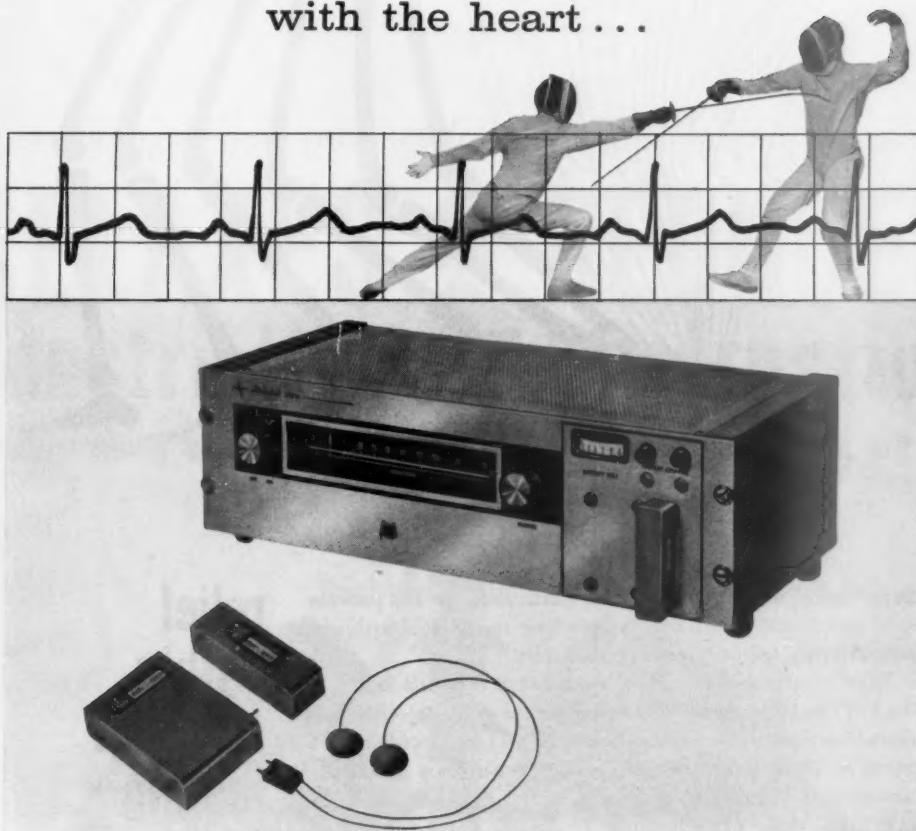
DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.). This is the usual adult dose.

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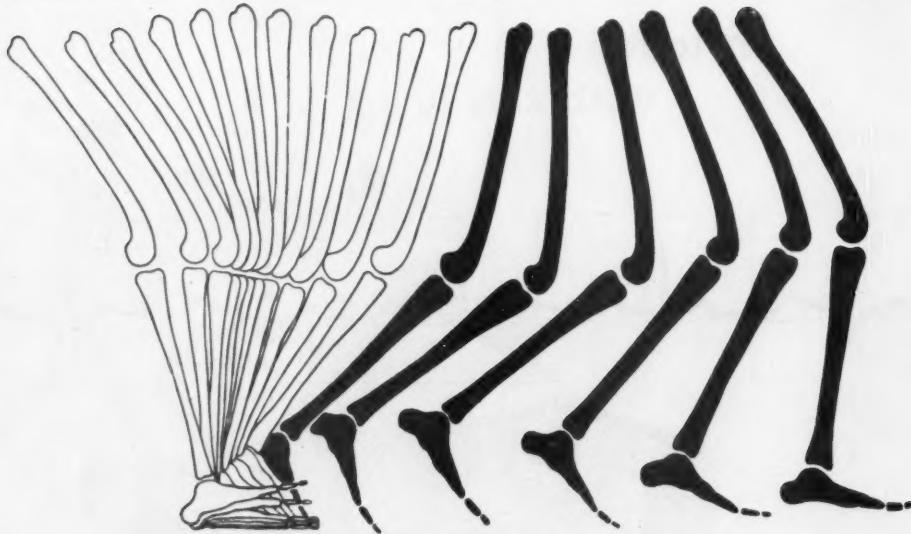
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Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.¹ "Post-injection flare-up was practically non-existent."¹

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.

Each cc. contains:

Medrol (methylprednisolone)	40 mg.
acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.
Supplied: 1 cc. and 5 cc. vials	
<i>20 mg. per cc.</i>	
<i>Each cc. contains:</i>	
Medrol (methylprednisolone)	
acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

- Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. 61:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off.
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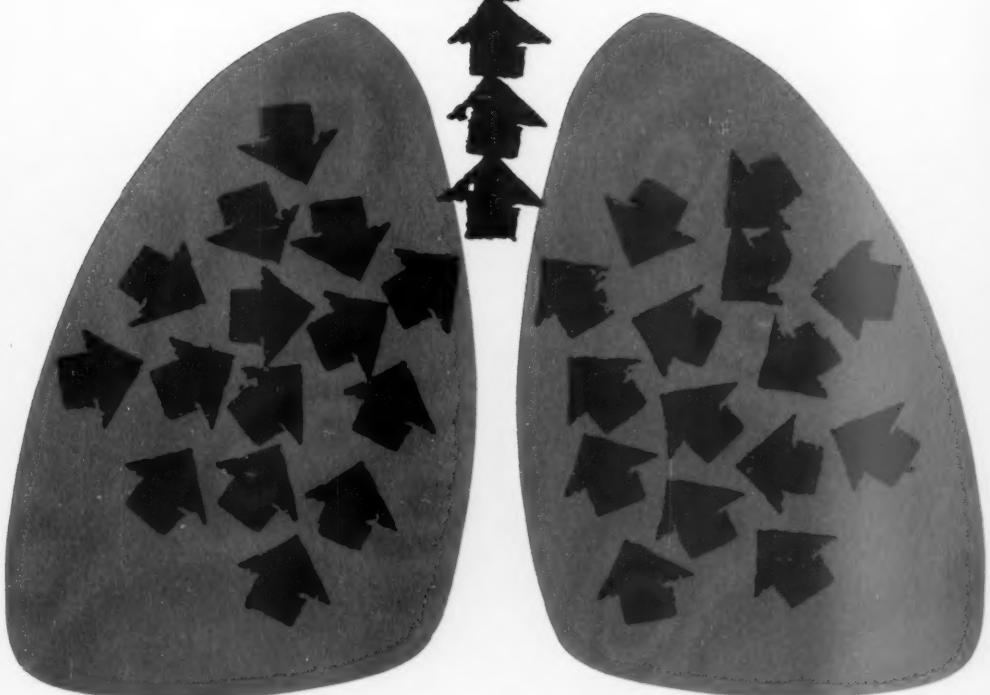
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by overcoming bronchospasm

due to tenacious mucus



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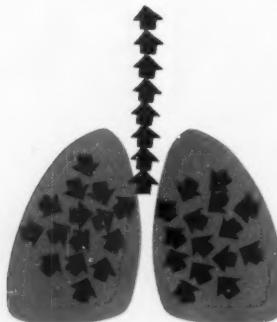
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BRONCHODILATOR - EXPECTORANT

RELAXES CONSTRICITION *by overcoming bronchospasm*

Theophylline overcomes bronchospasm through relaxation of the bronchiolar smooth muscle.

REDUCES OBSTRUCTION *due to tenacious mucus*

Glyceryl guaiacolate increases respiratory tract fluids which dilute the thick tenacious mucus in the bronchioles, facilitating its removal and thereby reducing obstruction.



combines the bronchodilator effectiveness of theophylline¹⁴

with the proved expectorant action of glyceryl guaiacolate¹⁵

formulated for flexible low-volume dosage

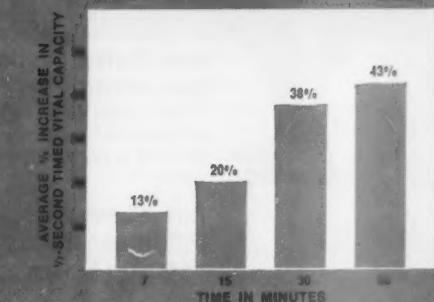
in a pleasant-tasting hydro-alcoholic vehicle for rapid absorption

QUIBRON RAPIDLY PROVIDES EFFECTIVE THEOPHYLLINE BLOOD LEVELS^{7,8}



Following administration of Quibron elixir at the recommended dosage for adults⁹ and children,¹⁰ effective blood levels of theophylline were reached within 15-30 minutes and maintained for more than four hours.

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Following administration of 20 ml. Quibron elixir, vital capacity was markedly improved, as measured by the timed 1/2-second method. Pulmonary function tests confirmed the clinical observation of rapid relief occurring in 10-15 minutes in most patients.¹¹

Indications: Bronchial asthma, asthmatic bronchitis, chronic bronchitis and pulmonary emphysema.

Dosage & Administration: Adults: 1 to 2 tablespoons, 2-3 times daily. Children, 6-12: 1 tablespoon, 2-3 times daily. (Children weighing over 100 lbs. may require adult doses.) Children under 6: 1/2 teaspoon per 10 lbs. body weight, 2-3 times daily. During the first day of treatment, especially in severe attacks, the usual dose may be increased by one half.

Side Effects: Theophylline may cause gastric irritation, with possible abdominal discomfort, nausea and vomiting. The administration of Quibron elixir after meals may help avoid such symptoms. Theophylline may also exert some stimulating effect on the central nervous system.

Cautions: Quibron elixir should not be administered more frequently than every 6 hours or within 12 hours after rectal administration of any preparation containing theophylline or aminophylline. Other formulations containing xanthine derivatives should not be given concurrently with Quibron elixir.

Supplied: Each tablespoon of Quibron elixir (15 ml.) contains theophylline 150 mg. and glyceryl guaiacolate 90 mg. in a 15% hydro-alcoholic vehicle. Bottles of 8 fl. oz.

References: (1) Schluger, J.; McGinn, J. T., and Hennessey, D. J.: Am. J. M. Sc. 233:296-302 (March) 1957. (2) McLaren, W. R.: California Med. 91:278-282 (Nov.) 1959. (3) McLaren, W. R.: Ann. Allergy 77:729-739 (Sept.-Oct.) 1959. (4) Spielman, A. D.: Ann. Allergy 13:270-276 (May-June) 1957. (5) Gau, L. J., and Frederick, W. S.: Am. Pract. & Digest. Treat. 2:844-851 (Oct.) 1951. (6) Schwartz, E.; Levin, L.; Leibowitz, H., and McGinn, J. T.: Am. Pract. & Digest. Treat. 7:585-588 (April) 1956. (7) Schiller, L. W., and Goldman, G.: Personal communication on file at the Mead Johnson Research Center.¹² (8) Levin, S. J., and Weissig, J.: Personal communication on file at the Mead Johnson Research Center.¹³ (9) Puls, R. J., and Grater, W. C.: Current Therap. Res., in press (Nov.) 1961.

*These data are available to physicians on request.



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Kolantyl is so much more than an antacid

Examine the KOLANTYL Formula:
antispasmodic: BENTYL (dicyclomine) Hydrochloride
antacids: Magnesium Oxide/Aluminum Hydroxide Gel **demulcent:** Methylcellulose **anti-enzyme:** Sodium Lauryl Sulfate

References: 1. Altuchula, M. D.: *M. Sc.* 6:360, 1959.
 2. Rubin, J. M.; Baylin, G. J.; Legeron, C. W., and Texter, E. C., Jr.: *Gastroenterology* 33:252, 1953.
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 4. Kasich, A. M.; Bolesman, A. F., Jr., and Rafsky, J. C.: *Am. J. Digest. Dis.* 1:361, 1956. 5. Roth, J. L. A.; Wechsler, R. L., and Beckus, H. L.: *Gastroenterology* 31:493, 1956. 6. Rafsky, J. D.: *Gastroenterology* 27:29, 1954.

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Distinguished by high potency and its ability to maintain a uniform response with a constant single daily dose, Sintrom is particularly suited to long-term therapy. Significantly more rapid and transient in action, Tromexan is well adapted to cases calling for more immediate control of thrombotic tendencies.

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Sintrom®, brand of acenocoumarol, is supplied as double-scored tablets of 4 mg.

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Tromexan®: for ultra-rapid action with ready reversibility of effect

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Why arthritic patients feel much better on Dianabol

1. In arthritis, Dianabol improves general physical condition

Arthritis, like other chronic illnesses, plunges the body into a catabolic state. Protein stores are depleted; appetite wanes; weight drops; strength and vigor decline. By aiding the deposition, synthesis and utilization of protein, and by conserving calcium, Dianabol promotes lean weight gain, increases strength and vitality, and strengthens bone structure in patients with a wide range of chronic diseases. Recent studies show that adjunctive use of Dianabol may be particularly valuable in patients with arthritis to improve over-all clinical status. Kuzell and Naugler,¹ for example, report that arthritic patients on Dianabol "generally have experienced an increase in appetite, weight, strength and endurance." Kuzell and Naugler note further: "Unlike some other testosterone derivatives, the use of this compound [Dianabol] is not followed by virilizing phenomena. Fluid retention has been no problem."

2. In arthritis, Dianabol helps restore a sense of well-being

Plagued by pain and reduced mobility, arthritics often lose hope and become depressed. The marked improvement in general health usually associated with therapy with Dianabol may have a favorable effect in these patients, as it has in so many chronically ill individuals. As physical status improves, hope is revived and a sense of well-being restored. Commenting on the use of Dianabol in a group of debilitated, cachectic patients, Gingrich² states: "The majority of patients experienced increase in appetite and a feeling of well-being."

3. In arthritis, Dianabol augments the beneficial effects of salicylates, corticosteroids, etc.

Several investigators^{1,3,4} have observed improved therapeutic response after the addition of Dianabol to antiarthritis regimens. Kuzell and Naugler¹ state: "In generalized osteoarthritis, symptoms have been less bothersome, and in ankylosing spondylitis gain in weight and strength has followed the use of Dianabol." Clark,³ reporting on 12 hospitalized patients with rheumatoid arthritis being given moderate to large doses of corticosteroids with evidence of steroid intoxication, noted that the addition of Dianabol promptly decreased joint symptoms but increased steroid intoxication. However, with Dianabol it was possible to reduce corticosteroid dosage considerably, while maintaining and even furthering clinical improvement. In 15 ambulatory patients on small maintenance doses of corticosteroids, the addition of Dianabol resulted in further clinical improvement which was continued even when corticosteroid dosage was reduced in some cases.^{3,4}

4. In arthritis, Dianabol counteracts the catabolic effects of corticosteroids

Prolonged use of corticosteroids may result in excessive breakdown of protein in all tissues, including bone,⁵ as well as undue phosphorus and calcium loss.⁶ If protein destruction is allowed to go unchecked, it may lead to osteoporosis—a condition that has occurred with increasing frequency in patients receiving corticosteroids for extended periods.⁷ Tillis⁵ asserts that it is "imperative" to restore the protein bone matrix in such patients

through the use of an anabolic agent. He studied the specific anabolic benefits of Dianabol in 50 patients with osteoporosis (34 postmenopausal and 16 corticosteroid-induced), most of whom also had rheumatoid arthritis. Dianabol relieved bone pain, increased strength and vigor, and induced a sense of well-being in 41 (82 per cent) of these patients. Edema, observed in 8 patients, was cleared in 4 by reduction of dosage; the remaining 4 responded promptly to hydrochlorothiazide. Gastric distress was noted in 2 patients, slight hoarseness in 1 woman, and facial acne in 1 woman. Other investigators^{8,9} have shown that addition of Dianabol to the regimens of patients receiving corticosteroids improved nitrogen and potassium metabolism and reduced phosphorus and calcium losses. Reporting on 10 patients taking corticosteroids, most of whom had corticosteroid-induced osteoporosis and/or myopathy, Abbott⁹ states: "In the patients who showed a markedly negative nitrogen balance the administration of 10 mg. of Dianabol per day greatly reduced the protein deficit. In others who were eating well and taking smaller amounts of corticosteroids a positive nitrogen balance resulted which increased with Dianabol." Abbott notes that creatinuria, which occurred on corticosteroids alone, was increased by Dianabol, as it is by methyl-testosterone and the newer oral methyl- or ethyl-testosterone derivatives. However, he observes that the "significance of this creatinuria is not known and no ill effects have been ascribed to this change." While the finding of elevated serum aldolase levels raised the theoretical possibility of potentially deleterious effects, Vignos *et al*⁸ and Abbott⁹ noted no androgenic or myopathic effects and no liver disorders in patients who took Dianabol and corticosteroids for up to 8 months. Kuzell

and Naugler¹ state it is their impression that Dianabol has checked weight loss following prolonged administration of triamcinolone in patients with rheumatoid arthritis. They add that, with Dianabol, protein patterns have migrated toward normal profiles, purpura consequent to corticosteroid administration has been lessened, and the erythrocyte sedimentation rate has been diminished.

advantages of Dianabol over other anabolic agents as an adjunct in the treatment of arthritis

- *Dianabol has an exceptionally favorable anabolic/androgenic ratio.* The anabolic effects of Dianabol occur at dosages which generally preclude androgenic side reactions. In this respect, Dianabol has proved superior to 12 other anabolic compounds.¹⁰ Laboratory evidence also indicates that Dianabol has no estrogenic, progestational, or corticoid-like activity which might be clinically detrimental.
- *Dianabol is economical.* Low in cost, Dianabol is especially suitable for arthritic patients who usually require long-term therapy.
- *Dianabol is effective orally.* Because it is an oral preparation, Dianabol spares patients the inconvenience and discomfort of parenteral drugs.

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low-cost, oral anabolic agent

an important new ally in the treatment of arthritis

Other indications for Dianabol:

- Underweight, debility and weakness
- General physical weakness and cachexia due to chronic diseases
- Retarded convalescence from illness, surgery, fractures, wounds, and burns

For complete information about Dianabol (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N.J.

SUPPLIED: Tablets, 5 mg.
(pink, scored); bottles of 100.



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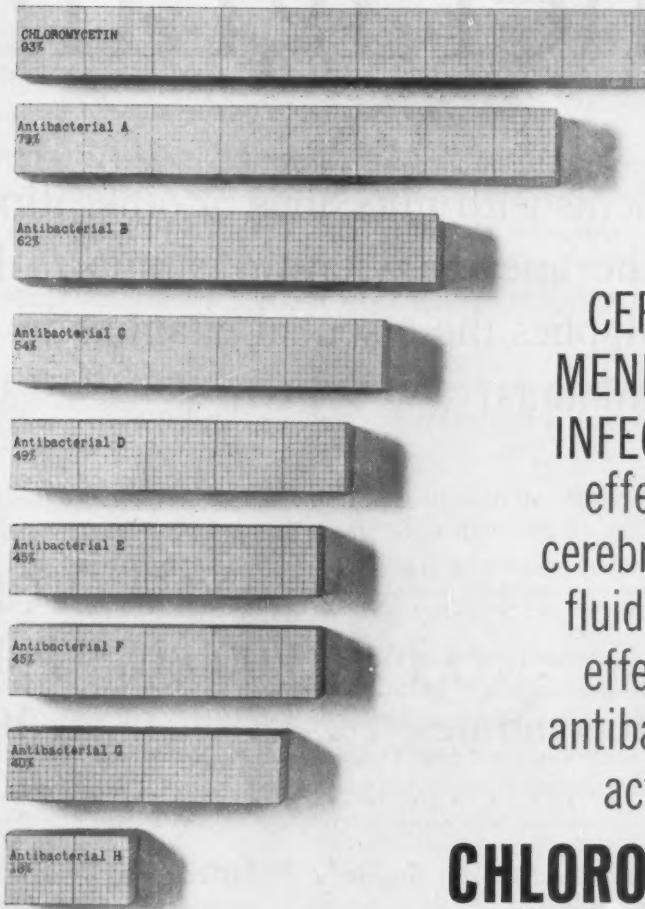
Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days.* (J.A. M.A. Vol. 172, No. 18, April 30, 1960.)

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Sensitivity tests were done by the disc method on a total of 100 strains of *H. influenzae* obtained on clinical isolates from 1955 through 1958.

*Adapted from Jolliff, C. R.; Engelhard, W. E.; Ohlsen, J. R.; Heidrick, P. J., & Cain, J. A.: *Antibiotics & Chemother.* 10:694, 1960, with permission of the authors.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapsseals® of 250 mg., in bottles of 16 and 100.

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“nutrition...present as a modifying or complicating factor in nearly every illness or disease state”¹

1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958

cardiac diseases “Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease.”² 2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

arthritis “It is our practice to prescribe a multiple vitamin preparation to patients with rheumatoid arthritis simply to insure nutritional adequacy . . .”³

3. Fernandez-Herlihy, L: Lahey Clinic Bull. 11:12 (July-Sept.) 1958.

digestive diseases Symptoms attributable to B-vitamin deficiency are commonly observed in patients on peptic ulcer diets.⁴ Daily administration of therapeutic vitamins to patients with hepatitis and cirrhosis is recommended by the National Research Council.⁵ 4. Sebrell, W. H.: Am. J. Med. 25:673 (Nov.) 1958. 5. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 57.

degenerative diseases “Studies by Wexberg, Jolliffe and others have indicated that many of the symptoms attributed in the past to senility or to cerebral arteriosclerosis seem to respond with remarkable speed to the administration of vitamins, particularly niacin and ascorbic acid. These facts indicate that the vitamin reserve of aging persons is lowered, even to the danger point, more than is the case in the average American adult.”⁶ 6. Overholser, W., and Fong, T.C.C. In Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 264.

infectious diseases Infections cause a lowering of ascorbic acid levels in the plasma; and the absorption of this vitamin is reduced in diarrheal states.⁷ 7. Goldsmith, G. A.: Conference on Vitamin C. The New York Academy of Sciences, New York City, Oct. 7 and 8, 1960. Reported in: Medical Science 8:772 (Dec. 10) 1960.

diabetes Diabetics, like all patients on restricted diets, require an extra source of vitamins.⁸ “Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet. . . . There is some evidence of interference with normal riboflavin utilization during catabolic episodes.”⁹

8. Duncan, G. G.: Diseases of Metabolism 4th edition W. B. Saunders, Philadelphia, 1959, p. 812. 9. Pollack, H.: Am. J. Med. 25:708 (Nov.) 1958.

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*U.S. Patent 2895881



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INVESTIGATOR

FINDINGS

DUNLOP, EDWIN:
The treatment of
depression in
private practice.

"Amitriptyline [ELAVIL] has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears... to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes."

"...Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders."

BENNETT, DOUGLAS:
Treatment of
depressive states
with amitriptyline.

"In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation. The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression."

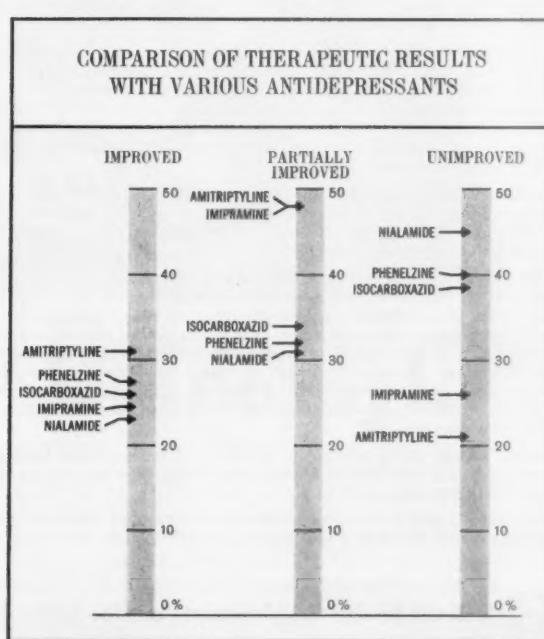
SAUNDERS, JOHN C.:
Antidepressives: the
pith of affective therapy.

"Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuro-psychiatric diseases.... Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75)."

OSTFELD, ADRIAN M.:
Effects of an anti-
depressant drug on tests
of mood and perception.

"Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population."

INVESTIGATOR	FINDINGS
AYD, FRANK J., JR.: A critique of antidepressants.	<p>"Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine.</p> <p>"... Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments."</p>



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DEPRESSION**
(continued)

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INVESTIGATOR	FINDINGS
DORFMAN, WILFRED: Masked depression.	"In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%)."
FELDMAN, PAUL E.: Psychotherapy and chemotherapy (amitriptyline) of anergic states.	"Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings."

INDICATIONS: manic-depressive reaction—depressed phase; involutional melancholia; reactive depression; schizoaffective depression; neurotic-depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whether the emotional difficulty is a manifestation of neurosis or psychosis,¹ and in ambulatory or hospitalized patients.^{1,2,3}

USUAL ADULT DOSAGE: Tablets — initial dosage 25 to 50 mg. three times a day, depending on body weight, severity, and clinical disturbances. Dosage may be adjusted up or down depending upon the response of the patient. Some patients improve rapidly, although many depressed patients require four to six weeks of therapy before obtaining antidepressant response. For the ambulatory patient the dosage range for Tablets ELAVIL is 40 to 150 mg. daily. In the hospitalized patient, a daily dosage up to 300 mg. may be required. Injection ELAVIL may be given IM to rapidly calm depressed patients with symptoms of anxiety and tension while instituting therapy of the underlying depression. Initial therapy is 2 to 3 cc. (20 to 30 mg.) IM, q.i.d.

The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstated.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. It does, however, augment or may even potentiate the action of MAO inhibitors. Thus, in patients who have been receiving MAO inhibitors, ELAVIL should be instituted cautiously after the effects of the MAO inhibitors have been dissipated. No evidence of drug-induced jaundice, agranulocytosis, or extrapyramidal symptoms has been noted. Side effects with ELAVIL are seldom a problem and are not serious. They are dosage-related and have been readily reversible. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma, prostatic hypertrophy and urinary retention.

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Before prescribing or administering ELAVIL, the physician should consult the detailed information on use accompanying the package or available on request.



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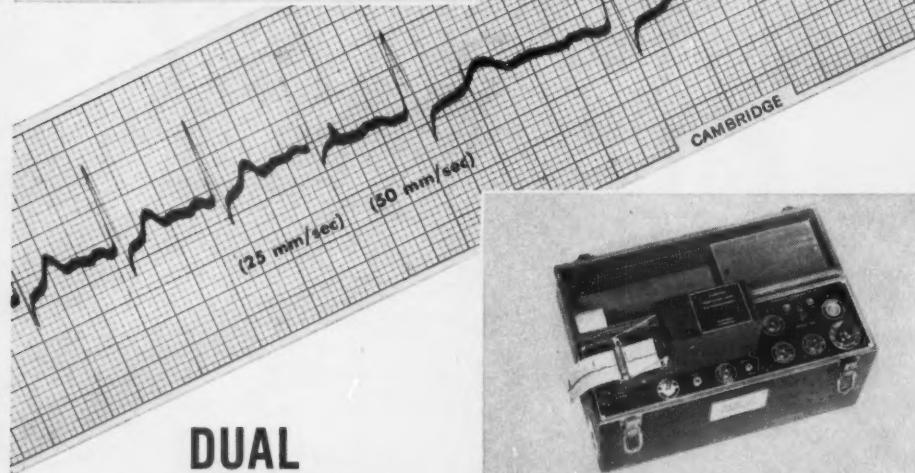
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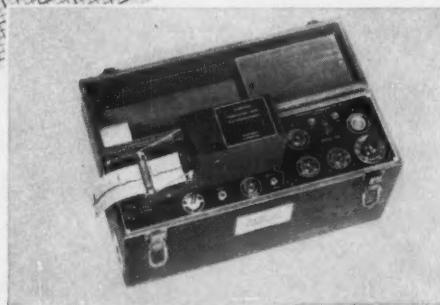


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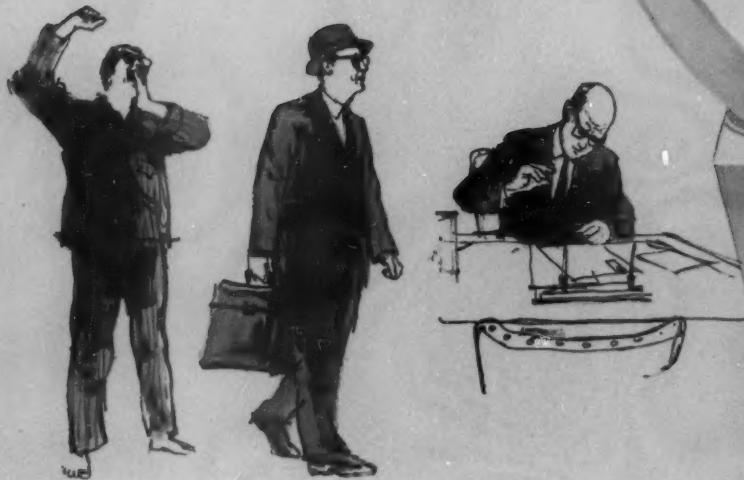


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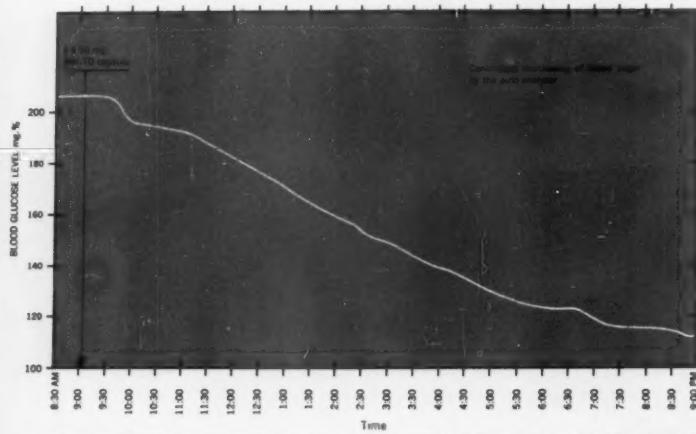
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administration and dosage: One 50 mg. DBI-TD capsule with breakfast regulates many stable adult diabetics. If higher dosages are needed, a second DBI-TD capsule is added to the evening meal, and further increments (at weekly intervals) to either the A.M. or P.M. dose. In patients requiring insulin, reduction of insulin dosage is made as DBI-TD dosage is increased, until effective regulation is attained. (The acidosis-prone, insulin-dependent diabetic should be closely observed for "starvation" ketosis.) Sulfonylurea secondary failures usually respond to relatively low dosages of DBI-TD alone, or combined with reduced dose of sulfonylurea.

side effects: Gastrointestinal reactions occur infrequently and are usually associated with higher dosage levels. They may include unpleasant, metallic taste in the mouth, continuing to anorexia, nausea, and, less frequently, vomiting and diarrhea. They abate promptly upon reduction of dosage or temporary withdrawal. In case of vomiting, DBI-TD should be withdrawn immediately.

precautions: Particularly during the initial period of dosage adjustment, every precaution should be observed to avoid acidosis and coma or hypoglycemic reactions. Hypoglycemic reaction has been observed on rare occasions in the patient treated with insulin or a sulfonylurea in combination with DBI-TD. "Starvation" ketosis, that is the appearance of acetoneuria in the presence of a lowered or normal blood sugar, must be distinguished from "insulin-lack" ketosis which is accompanied by hyperglycemia and acidosis. A reduction in the dose of DBI-TD of 50 mg. per day (with a slight increase in insulin as required), and/or a liberalization in carbohydrate intake rapidly restores metabolic balance and eliminates the "starvation" ketosis. Do not increase DBI-TD dosage or give insulin without first checking blood and urine sugars.

caution and contraindication: As with any oral hypoglycemic therapy reasonable caution should be observed in severe preexisting liver disease. The use of DBI-TD alone is not recommended in the acute complications of diabetes: acidosis, coma, infections, gangrene or surgery.

Complete detailed literature is available to physicians.



New, more effective analgesic

Kills pain....stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions—new compound of Soma, phenacetin and caffeine kills pain, stops tension, reduces fever—gives more complete relief than other analgesics . . . acts fast, relief lasts four to six hours

Composition: 200 mg. Soma (carisoprodol), 160 mg. phenacetin, 32 mg. caffeine. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 apricot-colored, scored tablets.

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SOMA COMPOUND + CODEINE

Soma Compound boosts the effectiveness of codeine. **SOMA COMPOUND + CODEINE**

therefore contains only $\frac{1}{4}$ grain of codeine phosphate to relieve the more severe pain that usually requires $\frac{1}{2}$ grain. Otherwise, its composition—and dosage—is the same as Soma Compound. Supplied in bottles of 50 white, lozenge-shaped tablets.

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As a resuscitator, for short or long term use, or for emergency, it functions as an assist/guarantor. As an IPPB unit, for intermittent positive pressure breathing therapy, it matches in function and operation the familiar Bennett therapy units. The controls are simple and direct, and there is no interaction of settings for the operator to master.

We invite you to write for detailed literature or demonstration.



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IN MANY GASTROINTESTINAL DISORDERS, you may wish to try the simple measures first... dietary control, a good antacid, drastic reduction of smoking and drinking. Some of the less complicated gastrointestinal disorders will respond to this common-sense regimen. On the other hand, in many cases you will decide upon an anticholinergic. And while you're planning the over-all regimen, one conclusion probably becomes inescapable: any lasting improvement depends also on control of the emotional component.



FOR COMPREHENSIVE MANAGEMENT,

Librax combines two exclusive developments of Roche research in a single capsule: Librium, the successor to the tranquilizers and Quarzan, a superior new anticholinergic agent. Librax helps control the anxiety and tension so frequently associated with gastrointestinal disorders; does not cause diarrhea or other undesirable effects in the digestive tract. Quarzan offers effective antispasmodic-antisecretory action; produces fewer, less pronounced side reactions than other anticholinergic agents. Clinical trials have established the value of Librax specifically in the following conditions: peptic ulcer, gastritis, hyperchlorhydria, duodenitis, pylorospasm, ulcerative or spastic colitis, biliary dyskinesia, cardiospasm, and other functional or organic disorders of the gastrointestinal tract.



Each Librax capsule provides 5 mg Librium HCl and 2.5 mg Quarzan Br.

Consult literature and dosage information, available on request, before prescribing.

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LIBRIUM[®] — 7-chloro-2-methylamino-5-phenyl-1,4-benzodiazepine 4-oxide

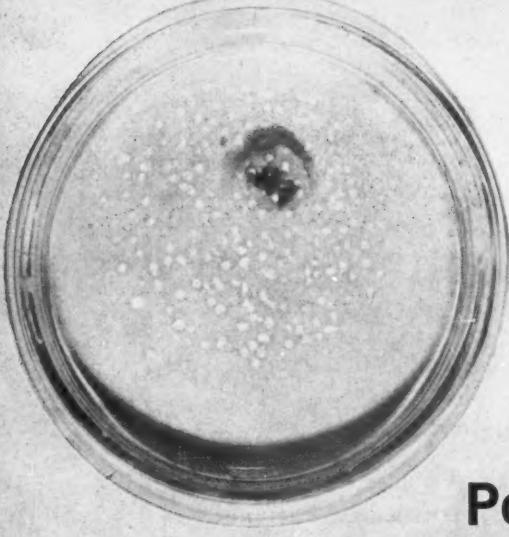
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NEW
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CAUSE-EFFECT THERAPY



Potassium Penicillin V versus semi-synthetic penicillin

Recent clinical evidence sheds new light on some important questions...

Q. Which of the two oral penicillins provides greater antibacterial activity?

In a follow-up study¹ of oral penicillins, McCarthy and Finland compared the antibacterial activity of potassium penicillin V and semi-synthetic penicillin. They said: "Penicillin V provided greater activity than phenethicillin [semi-synthetic penicillin] against the streptococcus and pneumococcus, at least equivalent activity against the staphylococcus and sarcina in the serum and the same or greater activity in the urine . . ."

In another study², Griffith found that penicillin V not only produced peak levels of serum antibacterial activity faster, but produced values almost half again as high as those obtained with semi-synthetic penicillin.

A direct laboratory comparison³ by Abbott scientists revealed a measurable difference in activity, milligram for milligram, between the two penicillins *in vitro*. Against four pathogenic strains (staphylococcus, streptococcus, pneumococcus, and corynebacterium species), potassium penicillin V exhibited from two to eight times the antibacterial activity of semi-synthetic penicillin.

Q. How valid are blood levels as a basis for comparison?

In comment on the two penicillins, McCarthy and Finland state¹: "Thus, although the claim of better absorption and excretion and higher serum level of phenethicillin may be partly correct, strictly speaking, this is true in a very restricted sense and is therapeutically meaningless. Indeed the claim is misleading since it clearly implies greater antibacterial and presumably curative activity, which, in fact, the drug does not possess . . ."

Q. Are there useful differences in resistance to penicillinase?

In another recent report⁴, Geronimus commented: "Very large concentrations [of semi-synthetic penicillin] . . . were required to inhibit even so-called

moderately penicillin-resistant staphylococci when populations were employed that approached those found *in vivo*. Inferences regarding the possible effectiveness of phenethicillin in infections by penicillinase-producing staphylococci drawn by others from experiments with relatively minute inocula were found to be unwarranted."

McCarthy et al.⁵ reached a similar conclusion: "Both of these penicillins [potassium penicillin V and phenethicillin] are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by *Staphylococcus aureus*."

At Abbott, investigators studying the same subject³ found that the rate of destruction of all three penicillins was so great that any differences were of no therapeutic significance.

Q. How does the safety of oral penicillins compare?

While surveys⁶ have established that oral penicillin produces fewer and less severe reactions than does injectable penicillin, to date no clinical studies have produced any evidence that one oral form is less allergenic than another.

Q. What about recent editorials on oral penicillin?

Recently, New England Journal of Medicine editorialized⁷: "It thus appears that the major claims of phenethicillin over penicillin V are not well founded. More data are needed to permit a complete comparison of these and other penicillins, particularly in their effects on infections caused by penicillinase-producing staphylococci, but it is fair to say that the new, so-called synthetic penicillin possesses no demonstrated virtue of importance that should impel one to choose over other available forms."

And in England, where semi-synthetic penicillin was first discovered and marketed, *British Medical Journal* editorialized⁸: "There is no evidence of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested."

Q. What are the benefits of Compocillin-VK?

Compocillin-VK is Abbott's potassium penicillin V. It offers early, high concentrations of serum antibacterial activity against penicillin-sensitive organisms. Following appropriate doses, initial activity levels are higher than those obtained with intramuscular penicillin G. Available in easy-to-take forms for any age: tiny Filmtab® tablets, 125 mg.; and 250 mg.; or as granules for tasty cherry-flavored Oral Solution.

COMPOCILLIN®-VK

(POTASSIUM PENICILLIN V)



1. McCarthy, C. G., and Finland, M., *New England J. Med.*, 263:315, Aug. 18, 1960. 2. Griffith, R. S., *Antibiot. Med. & Clin. Therapy*, 7:129, Feb., 1960. 3. Laboratory Records, Microbiology Dept., Abbott. 4. Geronomus, L. H., *New England J. Med.*, 263:315, Aug. 18, 1960. 5. McCarthy, C. G., Hirsch, H. A., and Finland, M., *Proc. Soc. Exper. Biol. Med.*, 103:177, Jan., 1960. 6. Welch, H., Lewis, C. N., Weinstein, H. I., Boeckman, B. B., *Antibiotics Annual*, 1957-58, p. 296. 7. Editorial: *New England J. Med.*, 263:361, Aug. 18, 1960. 8. Editorial: *Brit. M. J.*, 2:940, Nov. 7, 1959.

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strain...
anxiety...
hypertension
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*...controlled
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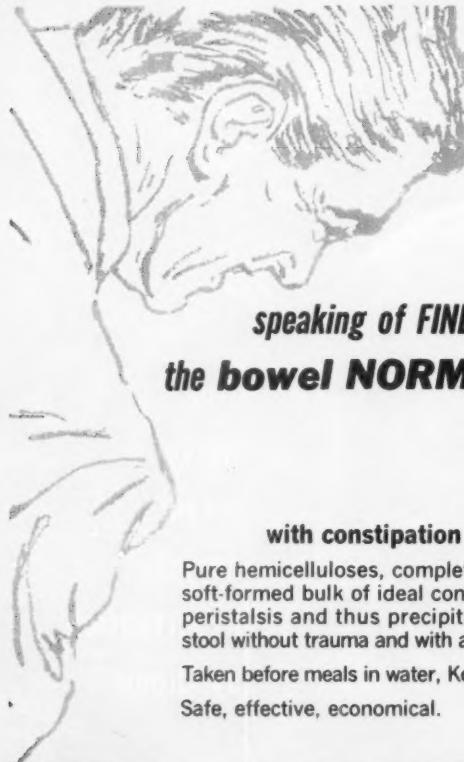
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BUTISOL relieves the tension and anxiety that contribute to hypertension—but without causing apathy or inertia. It leaves the patient capable of continuing normal activities.

BUTISOL has been shown¹ to be more effective with fewer side effects than other agents commonly used to control everyday nervousness, apprehension, tenseness and anxiety.

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1. Batterman, R. C.; Grossman, A. J.; Mountoff, G. J., and Leifer, P.: A Clinical Re-evaluation of Daytime Sedatives, Scientific Exhibit, Annual AMA Meeting, San Francisco, Calif., June 23-27, 1958.



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for the obese patient
with constipation or non-specific diarrhea

Pure hemicelluloses, completely calorie-free, producing a soft-formed bulk of ideal consistency to stimulate normal peristalsis and thus precipitate easy passage of a bland stool without trauma and with a minimum of peri-anal soiling.

Taken before meals in water, Konsyl helps to depress appetite.
Safe, effective, economical.



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for the thin, finicky patient
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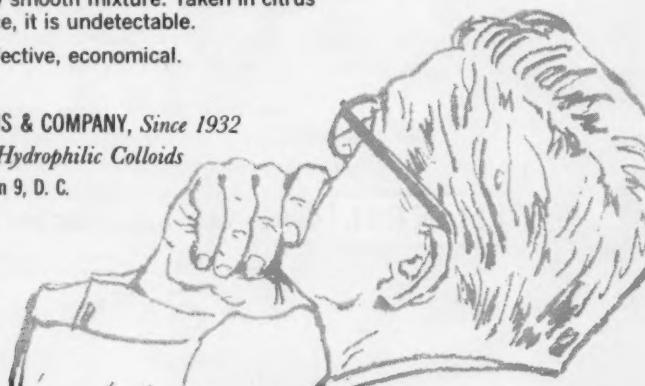
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fruit juice, it is undetectable.
Safe, effective, economical.

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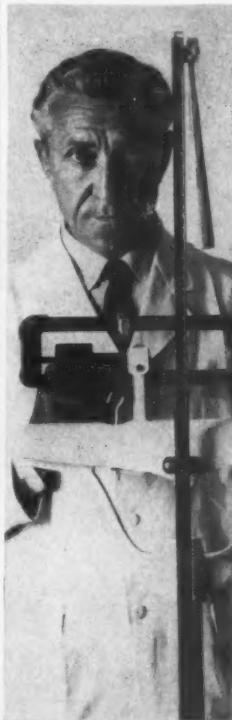
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Can we measure the patient's comfort?

Not objectively, as body weight can be measured on a scale.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

Alphadrol*



See page 91 for description, indications, dosage, precautions, side effects, and how supplied.

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ALLERGIC DISORDERS

RESPONSIVE TO TRIAMCINOLONE

"In general, triamcinolone was found a potent and useful corticosteroid for symptomatic control of allergic disease."*

■ enhanced anti-inflammatory, antiallergic, antipruritic effects ■ far less gastrointestinal distress ■ may be of value when other corticoids have failed ■ virtually no mood changes, edema, sodium or water retention, or secondary hypertension

Supply: Scored tablets of 1 mg., 2 mg. and 4 mg. Syrup, in 120 cc. bottles, each 5 cc. teaspoonful containing 5.1 mg. triamcinolone diacetate providing 4 mg. triamcinolone.

*Glaser, J.: Ann. Allergy 18:150 (May) 1960.

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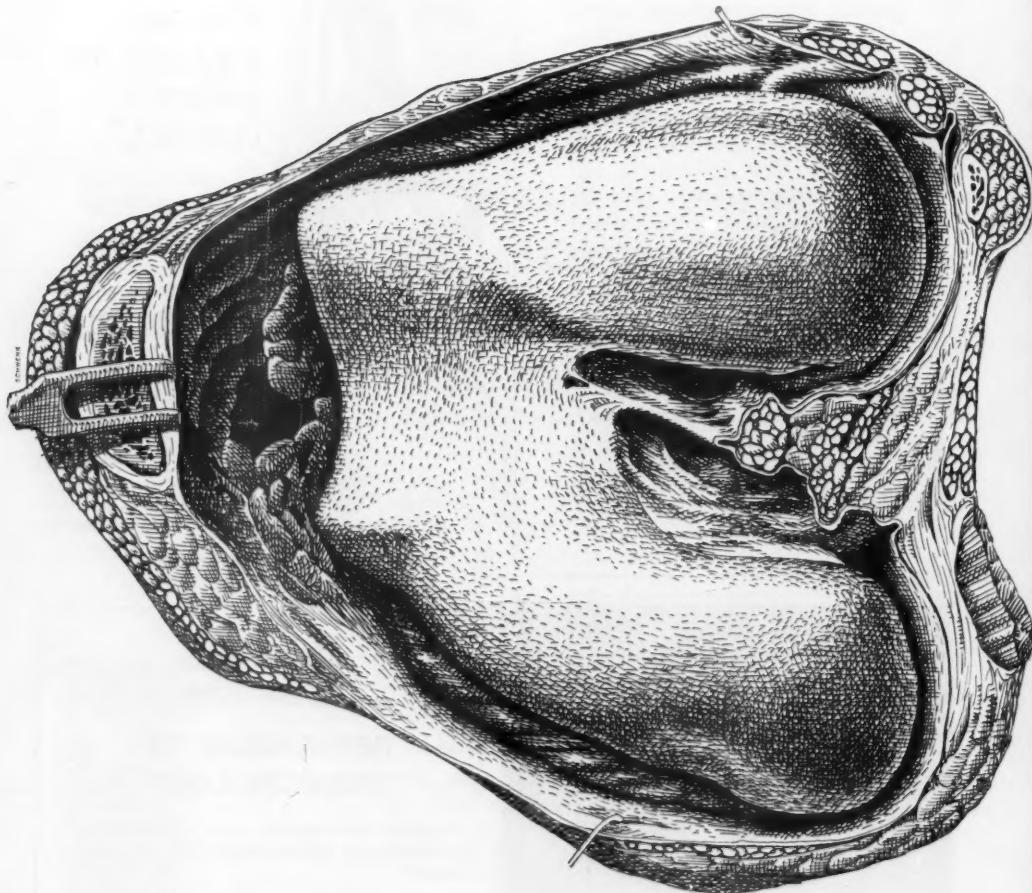
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Squibb Quality—the Priceless Ingredient

Asthma



because patients are more than arthritic joints, asthmatic lungs and inflamed skin . . . controlling inflammatory symptoms in steroid-responsive disorders is not enough!

Even cortisone, with its severe hormonal reactions, can effectively control allergic, inflammatory and rheumatoid symptoms. But a patient is more than the sum of his parts—and the joint, lung and the skin are only parts of a whole patient. Symptomatic control is but one aspect of modern corticotherapy, because what is good for the symptom may also be bad for the patient.

ARISTOCORT . . . An Outstanding "Special Purpose" Steroid when the complicating problem is increased appetite and weight gain . . .

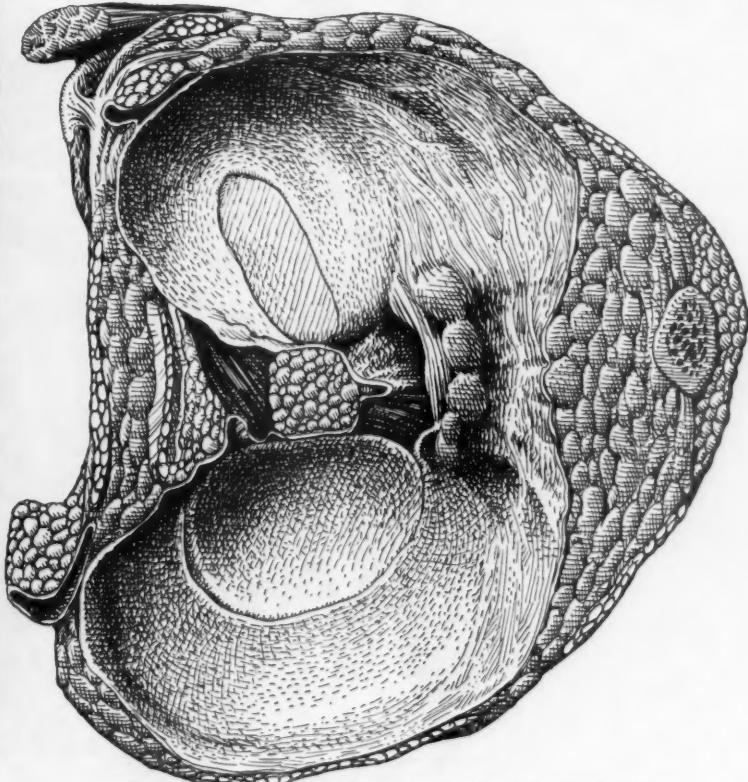
ARISTOCORT has been found to be a most useful steroid when the problem of appetite and weight control in middle-aged people, who all too often are overweight, can be serious; for patients where there already is difficulty with breathing; in patients where extra weight is still another burden on joints; in patients when a dietetic regimen must be carefully maintained, or weight gain makes diabetic control more difficult.

ARISTOCORT, in contrast to other steroids, does not stimulate the appetite and does not

*Unsurpassed "General Purpose" and "Special Purpose" Corticosteroid...
Outstanding for Short- and Long-term Therapy...*

Aristocort®

Triamcinolone Lederle



cause weight gain. In certain patients, there may even be a desirable suppression of appetite with ARISTOCORT, and in some patients who had gained weight on other steroids, there was less appetite stimulation with ARISTOCORT.¹⁻⁶

When the complicating problem is sodium retention or edema... Edema is, of course, undesirable in any patient. But salt and water retention is a particularly serious complication in patients with cardiac disease, hypertension, pulmonary fibrosis or renal dis-

order. This complication has often prevented the use of corticosteroids in patients with steroid-responsive disorders.

More than four years of extensive experience with ARISTOCORT have now demonstrated decisively that such patients can be treated effectively in indicated conditions, without this hazard.

Thus, Boland² reported that triamcinolone has less tendency than any other available steroid for salt and water retention; Hol-



lander¹ found triamcinolone useful in the treatment of patients with cardiac decompensation who needed steroid therapy since it did not produce edema,² and a similar statement was made by McGavack *et al.*³ Fernandez-Herlihy,⁴ among other investigators, has reported that triamcinolone brought on diuresis and sodium loss in patients with edema induced by earlier steroids or other causes.

When the complicating problem is emotional disturbance or insomnia ... Ill people are

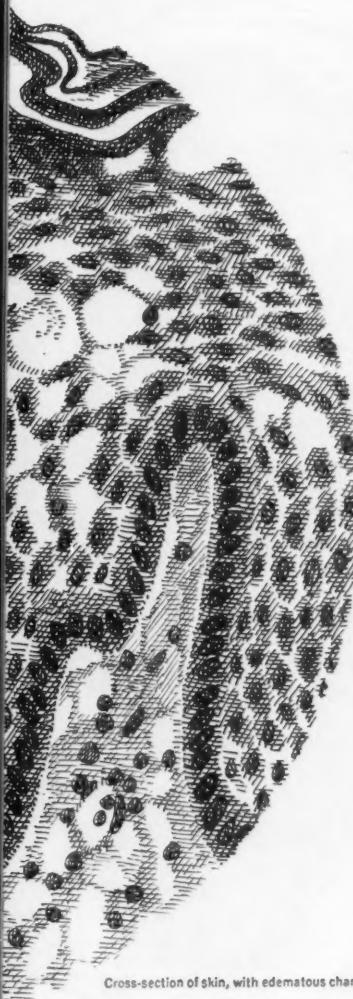
often emotionally disturbed. Euphoria and insomnia have been classic by-products of steroid therapy, except for ARISTOCORT. Psychic aberration and insomnia, intensifying itching and harmful scratching, have often accompanied other steroid therapy.^{1,3,4,5}

ARISTOCORT has been repeatedly singled out for the remarkably low incidence of mental stimulation and insomnia with its use.^{1,3,4,5} This important attribute means that patients with emotional and nervous disorders, who also have steroid-responsive conditions, can

*Unsurpassed "General Purpose" and "Special Purpose" Corticosteroid...
Outstanding for Short- and Long-term Therapy...*

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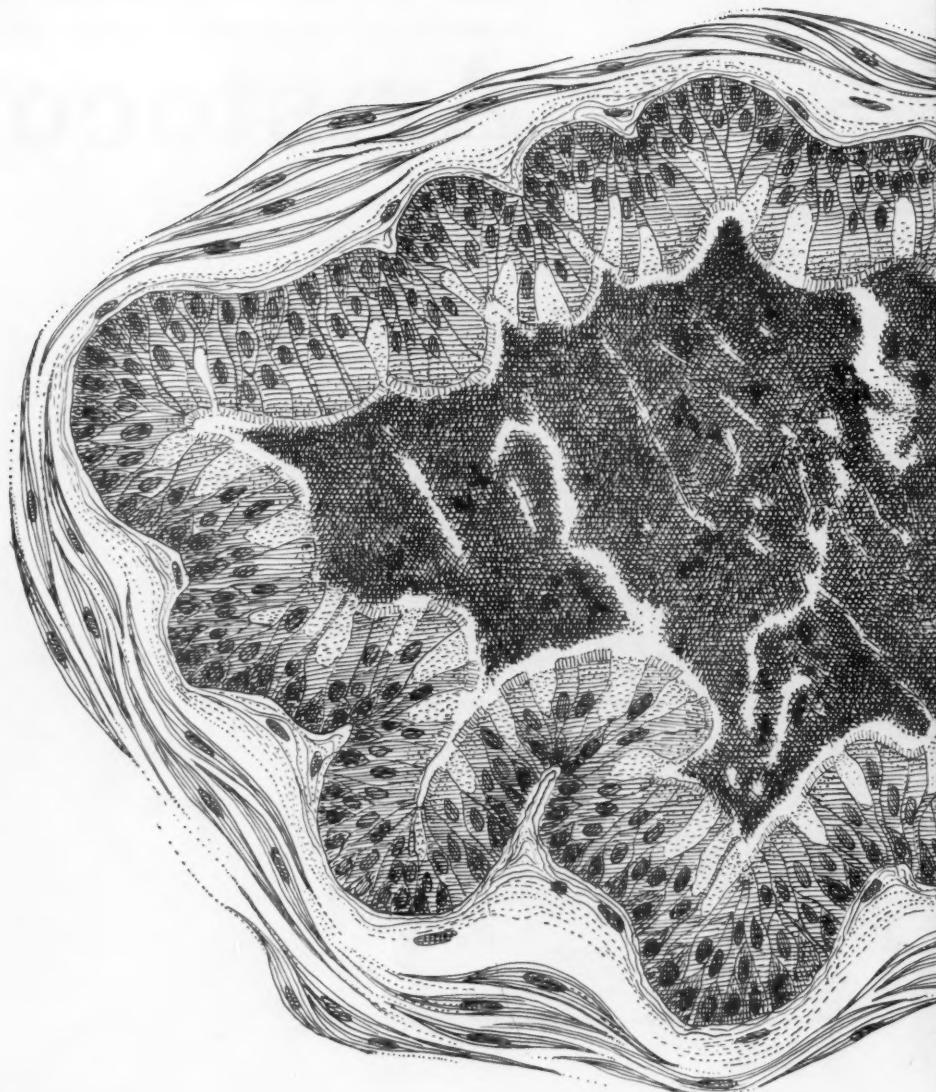
Cross-section of skin, with edematous changes, including vacuolization

be treated effectively with ARISTOCORT, with minimal risk of psychic stimulation.

When the complicating problem is hypertension... Hypertensive patients with conditions indicating steroid therapy, who were formerly considered unsuitable candidates for corticosteroids, can be treated with ARISTOCORT without the danger of increasing hypertension. Boland² states that triamcinolone has little or no tendency to aggravate arterial hypertension. Sherwood and Cooke⁹ found no blood pressure increase in any patient treated

with ARISTOCORT. In some, blood pressure even fell, and of these, three had been hypertensive. Kanof *et al.*¹⁰ reported that when ARISTOCORT was given to patients for long periods, there were no significant changes in blood pressure.

ARISTOCORT ... Unsurpassed "General Purpose" Corticosteroid Outstanding For Short-Or Long-Term Use... A substantial body of literature now attests to the unsurpassed efficacy and relative safety of ARISTOCORT in the treatment of acute conditions, requir-



ing short-term steroid therapy, and for chronic disorders, requiring prolonged use of steroids, often for a number of years.

A recent statement by an allergist, who described himself in his report as following a "middle course" in corticosteroid therapy may be taken as a representative example.¹¹ "... I have utilized this corticoid [triamcinolone] more than others previously prescribed, and for the time being at least, it is the corticoid of first choice. Since the introduction of triamcinolone, other corticoids including

dexamethasone and methylprednisolone have been introduced into clinical use and their superior virtues extolled. I have had only a limited experience with these corticoids, and therefore cannot pass critical judgment. In the few cases in which I have used them, they did not seem to offer any special advantage over triamcinolone, although this is hard to evaluate . . ."

An important point made by this investigator was that ARISTOCORT was used in conjunction with other drugs, such as iodides, expec-

*Unsurpassed "General Purpose" and "Special Purpose" Corticosteroid...
Outstanding for Short- and Long-term Therapy...*

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Cross-section of asthmatic bronchiole; lumen filled with exudate

torants, and bronchodilators. ARISTOCORT dosage could thus be reduced gradually to a relatively small daily maintenance dose. A similar recommendation was made for using antihistamines with corticoids to maintain the patient symptom-free on reduced corticoid dosage.

References: 1. Hollander, J. L.: *J.A.M.A.* 172:306 (Jan. 23) 1960. 2. Boland, E. W.: *J.A.M.A.* 174:835 (Oct. 15) 1960. 3. McGavack, T. H.: *Nebraska M. J.* 44:377 (Aug.) 1959. 4. Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 (June) 1958. 5. Cahn, M. M., and Levy, E. J.: *Am. Pract. & Digest Treat.* 10:993 (June) 1959. 6. McGavack, T. H.; Kao, K. Y. T.; Leake, D. A.; Bauer, H. G., and Berger, H. E.: *Am. J. M. Sc.* 236:720 (Dec.) 1958. 7. Fernandez-Herlihy, L.: *M. Clin. North America* 44:509 (Mar.) 1960. 8. McGavack, T. H.: *Clin. Med.* 6:997 (June) 1959. 9. Sherwood, H., and Cooke, R. A.: *J. Allergy* 28:97 (Mar.) 1957. 10. Kanof, N. B.; Blau, S.; Fleischmajer, R., and Meister, B.: *A.M.A. Arch. Dermat.* 79:631 (June) 1959. 11. Tuft, L.: *J.A.M.A.* 174:1801 (Dec. 3) 1960.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.



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...in over 1,000 published cases
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

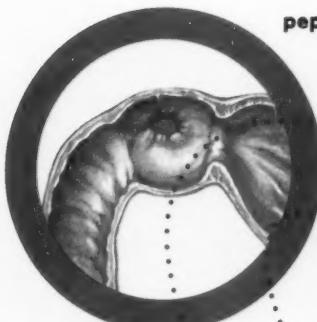
In
gastric disorders:
physician-preferred
agents to
relieve symptoms
and
promote recovery



hiatus hernia



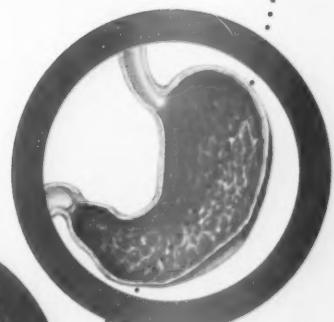
esophagitis



peptic ulcer



gastritis



gastric ulcer



in gastritis
topical anesthetic relieves

gastric discomfort

oxethazaine topically anesthetizes the mucosa in both
the acid stomach and alkaline esophagus

- new OXAINE M minimizes risk of constipation—

Palatable and well tolerated OXAINE M promotes good
patient cooperation and comfort.



**THERAPEUTIC EFFICACY IN CLINICAL TRIALS
in gastritis¹, esophagitis², peptic ulcer^{3,4}, irritable bowel
syndrome⁵ and related disorders**

Schwartz and Spertus⁶ used oxethazaine in alumina gel for hiatus hernia, esophagitis and gastritis in patients whose conditions were difficult to control without surgical intervention. Oxethazaine in alumina gel (with diet and anticholinergics) was significantly effective in these patients. The authors believe that surgery may often be avoided by the use of OXAINE in these difficult gastrointestinal problems.

OXAINE and OXAINE M were used in a series of patients referred because of lack of success with conventional therapy for complicated gastrointestinal problems. Of 56 patients, good to fair response was reported with OXAINE and OXAINE M. "In all cases there was no lasting improvement until oxethazaine was added to the regimen."⁸ OXAINE and OXAINE M were adjudged useful adjuncts to the medical management of peptic ulcer, gastroduodenitis and esophagitis, hiatus hernia, exaggerated gastrocolic reflex, and achalasia.

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Oxethazaine in Alumina Gel with Magnesium Hydroxide, Wyeth

OXAINE M is a demulcent, antacid, topical anesthetic. An improved formulation, OXAINE M contains magnesium hydroxide, alumina gel, and oxethazaine for relief of discomfort with minimal possibility of constipation.

Oxethazaine—the potent topical anesthetic in OXAINE M—is 500 times more potent topically than cocaine. Oxethazaine is evenly distributed over the gastric mucosa by the alumina gel vehicle and its action is prolonged. Oxethazaine is stable in gastric contents; its effectiveness and duration of action are almost unaltered despite changes in gastric pH.

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References: 1. Deutsch, E., and Christian, H.J.: J. Am. Med. Assoc. *169*:2012 (April 25) 1959. 2. Jankelson, I.R., and Jankelson, O.M.: Am. J. Gastroenterol. *32*:636 (Nov.) 1959. 3. Moffitt, R.E.: Rhode Island Med. J. *44*:151 (March) 1961. 4. Hollander, E.: Am. J. Gastroenterol. *34*:613 (Dec.) 1960. 5. Jankelson, O.M., and Jankelson, I.R.: Am. J. Gastroenterol. *32*:719 (Dec.) 1959. 6. Schwartz, I.R., and Spertus, I.: Scientific Exhibit, A.A.G.P., Miami Beach, April 16-20, 1961.

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basic antacid
therapy
for peptic ulcer

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Suspension and Tablets:
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- relieves pain
- neutralizes gastric acidity in range of pH 3 to 5
- inactivates pepsin and promotes healing
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comprehensive
therapy
for peptic ulcer

three beneficial actions: antacid
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Suspension and Tablets: Aluminum Hydroxide with
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- relieves pain
- calms emotional distress
- controls acidity
- inhibits gastric motility
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Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. et al.: *Circulation* 17:945, May 1958. 2. Friedlander, H. S.: *Am. J. Cardiol.* 1:395, Mar. 1958. 3. Riesman, J.E.F.: *New England J. Med.* 261:1017, Nov. 12, 1959. 4. Russek, H. I. et al.: *Circulation* 12:169, Aug. 1955. 5. Russek, H. I.: *Am. J. Cardiol.* 3:547, April 1959. 6. Tortora, A. R.: *Delaware M. J.* 30:298, Oct. 1958. 7. Waldman, S. and Peiner, L.: *Am. Pract. & Digest Treat.* 8:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. before meals and at bedtime, according to individual requirements.

GML-2619

Miltate®

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the
blood pressure
swing

Rautrax-N lowers high blood pressure gently, gradually...protects against sharp fluctuations in the normal pressure swing. Rautrax-N offers all the advantages of Raudixin, Naturetin and potassium chloride in a single dosage form *plus*:

increased efficacy—Combined action of Raudixin and Naturetin results in a potentiated antihypertensive effect greater than that produced by either drug alone.

increased safety—Potentiated action permits lower dose of other antihypertensive agents, thus reducing severity of side effects. Protection against possible potassium depletion.

flexibility—Interchangeable with either Raudixin or Naturetin \pm K.

economy—Maintenance dosage of only 1 or 2 tablets daily for most patients.

convenience—Once-a-day maintenance dosage. Two potencies available.

Supply: Rautrax-N—capsule-shaped tablets providing 50 mg.

Raudixin, 4 mg. Naturetin and 400 mg. potassium chloride.

Rautrax-N Modified—capsule-shaped tablets providing 50 mg.

Raudixin, 2 mg. Naturetin and 400 mg. potassium chloride.



Rautrax - N*

Squibb Standardized Whole Root Rauwolfia Serpentina (Raudixin) and Bendroflumethiazide ("Naturetin") with Potassium Chloride

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Squibb Quality—
the Priceless Ingredient

For full information,
see your Squibb
Product Reference
or Product Brief.

**BLOATING, BORBORYGMUS,
BELCHING, FLATULENCE**



**New! For pain, distention and distress
due to gastrointestinal gas!**

Bloating, belching, borborygmus or flatulence—whatever the symptoms of gastrointestinal gas, Phazyme provides uniquely effective relief. Phazyme is the first comprehensive treatment for gastrointestinal gas that combines both digestive enzymes and gas-releasing agents—dual action that provides far better results than either agent alone. Digestive enzymes minimize gas formation resulting from digestive disorders or food intolerance. The gas-releasing agent, specially activated dimethyl polysiloxane, breaks down gas-enveloping membranes—prevents gas entrapment. A two-phase tablet,

Phazyme releases these active components in the environments best suited to their actions—stomach or small intestine.

Phazyme is ideal medication for relieving gas distress in patients on the currently popular 900-calories-a-day diet. It is also recommended as routine therapy for cardiac patients to prevent gas from aggravating, complicating or simulating angina.

DOSAGE: One tablet with meals and upon retiring, or as required. SUPPLIED: As two-phase release, pink tablets, in bottles of 50 and 100.

REED & CARNRICK / Kenilworth, New Jersey 

minimizes gas formation • prevents gas entrapment

**PHAZYME™
TABLETS**

When anxiety adds to the gas problem—

Phazyme with Phenobarbital

The Phazyme formula with $\frac{1}{4}$ gr. phenobarbital. Supplied in bottles of 50. Phenobarbital may be habit forming.

new...
prolonged
antipruritic action
in a pleasant-tasting
chewable tablet

tacaryl® chewable tablets

METHDILAZINE, MEAD JOHNSON

prolonged antipruritic / antiallergic action...
not dependent on delayed intestinal release

Itching in children can now be controlled on b.i.d. dosage with a long-acting¹ antipruritic/antiallergic chewable tablet your pediatric patients will enjoy taking. They can also benefit by the effectiveness of Tacaryl Hydrochloride in controlling symptoms in a wide variety of allergic conditions,²⁻⁸ including hay fever and perennial rhinitis.

dosage: One Chewable Tablet (3.6 mg.) twice daily. Adjustment of dose or interval may be desirable for some patients.

contraindications: There are no known contraindications.

side effects: Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

cautions: If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence... though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

supplied: Pink tablets, 3.6 mg., bottles of 100.

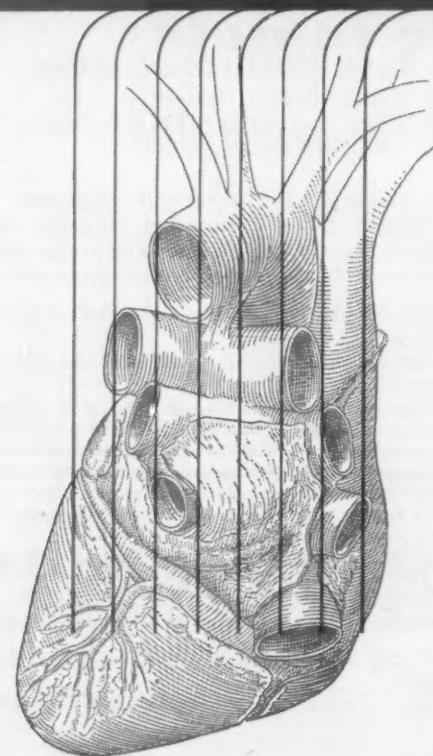
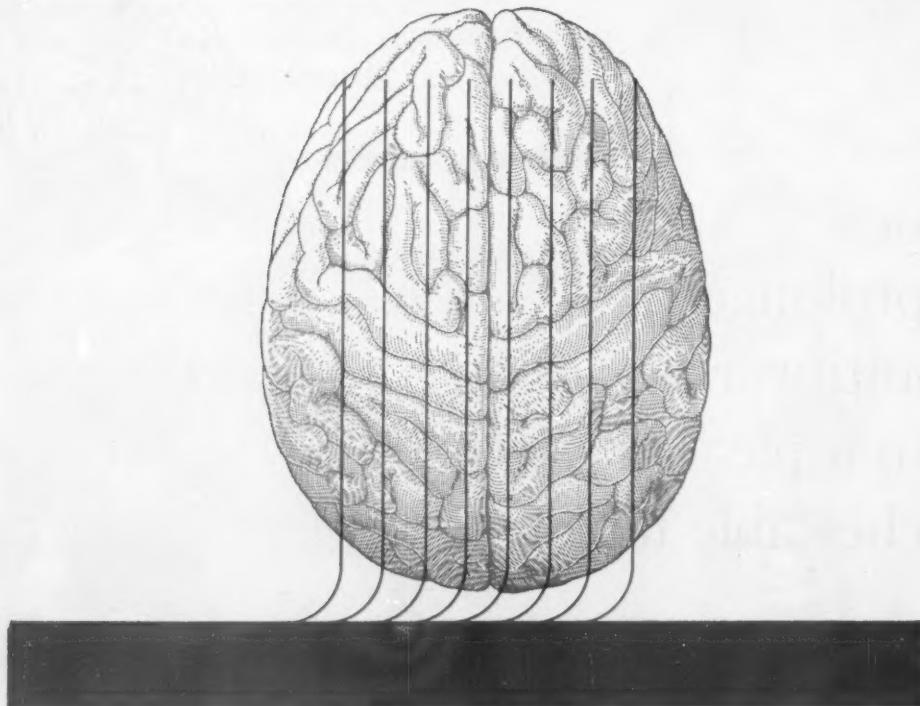
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To lift depression

Marplan covers the broad range of depressive states, including seemingly mild but progressively deteriorating conditions, many "masked" depressions, suicidal ideation, as well as depressions necessitating hospitalization. It increases accessibility of the withdrawn or regressed individual, improving rapport between physician and patient.

Where prior therapy has failed, Marplan often produces dramatic results. Prompt social recovery, e.g., was achieved with Marplan in a "severe, chronic, obsessive-compulsive neurotic illness" of 20 years' duration, disabling the patient for 12 years; previous treatment had included tranquilizers and ECT.⁶

A single agent, with two distinct primary effects, for two important clinical indications

Marplan

a happy balance of potency/safety

To control pain in "difficult" cases of angina pectoris

Marplan prevents anginal pain,¹⁻³ increases exercise tolerance^{2,4,5} and reduces nitroglycerin requirements.^{2,3} It is designed for use on a continuous schedule by patients with moderately severe to intractable angina pectoris.

Marplan improves the mental climate: Not only could anginal patients placed on Marplan "... do more than formerly ..." but they also felt better, were more alert, more cheerful.^{2,4} The loss of pain as a warning signal against undue exertion may be balanced by close patient supervision, strict guidance, and by maintaining all restrictions of activity in force prior to Marplan therapy.

Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. One might expect such potency to be associated clinically with increased side effects. Actually, Marplan strikes a happy balance of potency and safety, exhibiting a marked decrease in certain of the hydrazine side reactions; there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed.

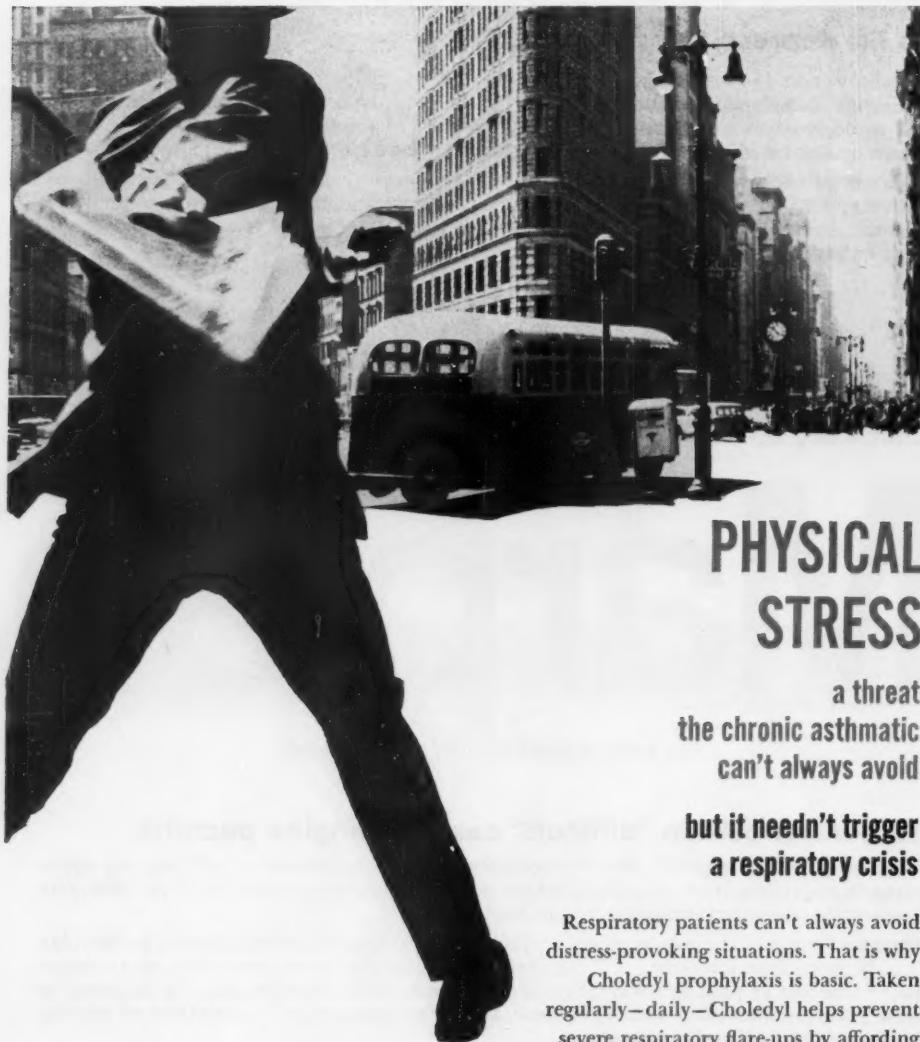
Consult literature and dosage instructions, available on request, before prescribing.

Selected bibliography from 38 published papers: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, Virginia M. Month., 87:23, 1960. 4. G. C. Griffith, Clin. Med., 6:1555, 1959. 5. G. C. Griffith, Dis. Nerv. System, 21:(Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, Dis. Nerv. System, 20:(Suppl.), 26, 1959.

MARPLAN® - 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine



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Respiratory patients can't always avoid distress-provoking situations. That is why

Choledyl prophylaxis is basic. Taken regularly—daily—Choledyl helps prevent severe respiratory flare-ups by affording sustained bronchodilatation.

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Precautions: Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. Full dosage information, available on request, should be consulted before initiating therapy.

to avoid the crisis in chronic bronchitis, chronic asthma, emphysema

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acetophenazine dimaleate

new calming agent with mild sedative effect

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- helps the cardiac or hypertensive patient slow down to the safer pace you recommend
- controls the agitation and tension that aggravate his condition^{1,2} ■ calms the patient and helps him get to sleep more easily ■ relatively free of side effects¹⁻³ ■ low in cost, particularly when long-term or adjunctive therapy is indicated

dosage: Total daily dosage may range from as low as 40 mg. (one 20 mg. tablet twice daily) to as high as 80 mg. daily. Generally, the most effective dosage is 20 mg. t.i.d. In those patients who have difficulty sleeping, the last tablet should be taken one hour before retiring.

supply: TINDAL Tablets, 20 mg., bottles of 100 and 1000.

references: (1) Hirshleifer, I.: Adjunctive therapy in cardiacs, presented at the Spring Scientific Symposium, Connecticut Acad. Gen. Pract., Hartford, Conn., March 16, 1961. (2) Frohman, I. P.: The Alleviation of Stress in the Elderly Cardiac Patient, *ibid.* (3) Kent, E. A.: Management of the Hyperactive Geriatric Patient, *ibid.*

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The enhanced POTABA + 6® is indicated in the treatment of scleroderma and other entities involving fibrosis. The significant antifibrosis action of POTABA® (Potassium p-Aminobenzoate, Glenwood) is here combined with Pyridoxine to help replenish the depleted stores of this essential vitamin in subjects with scleroderma.



In a series of 72 cases of scleroderma (1) 60 patients continued on POTABA for more than 3 months, and 58 of these had moderate to marked improvement, for a 97 PER CENT RESPONSE. There was no selection of the patients admitted to this series, each being placed on the program regardless of the severity of the disease (1).

1. Zarafonetis, Chris J. D.: Treatment of Scleroderma, Annals of Int. Med., 50:343-365 (1959)

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ATARAXOID contains the glucocorticoid prednisolone and the ataractic agent, hydroxyzine.

ADVANTAGES: ATARAXOID combines the tension-relieving effects of hydroxyzine with the anti-inflammatory action of prednisolone, a well-established corticosteroid, for superior control of the signs and symptoms of rheumatoid arthritis without unexpected side effects. An important result of the therapeutic effects of ATARAXOID is noted by Warter*: "In addition it was possible in many cases for the first time to gain the active cooperation of patients in the management of their disease."

INDICATIONS: Rheumatoid arthritis; other collagen diseases and related conditions; other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.); allergic states, including chronic bronchial asthma and severe hay fever; and allergic/inflammatory diseases of the skin and eyes.

ADMINISTRATION AND DOSAGE: ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: *Initial therapy*—4-6 ATARAXOID 5.0 Tablets. *Maintenance*—1-4 ATARAXOID 5.0 Tablets or 2-8 ATARAXOID 2.5 Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime.

SIDE EFFECTS: Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moon-face and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy.

PRECAUTIONS AND CONTRAINDICATIONS: Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

SUPPLIED: As green, scored ATARAXOID 5.0 Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored ATARAXOID 2.5 Tablets, containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

More detailed professional information available on request.

*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.

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ARTHRITIS RELIEVE BOTH THE
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new treatment “puts water to work” to relieve dry...itchy skin associated with internal disorders

Buffalo, N. Y. The discomforts of dry, itchy skin associated with internal disorders can now be relieved by Alpha-Keri, a new treatment that actually “puts water to work.” This is important because effective moisturizing of skin provides immediate symptomatic relief for most dryness and itching.

Several years were spent in developing Alpha-Keri. This new product is the first and only completely water-dispersible, antipruritic oil combining mineral oil and a skin moisturizer.* When added to bath water, Alpha-Keri turns milky white because this unique oil is emulsified immediately into microfine particles which are deposited over the entire skin area.

These microfine oil particles cling to the skin, forming a fine, invisible film that not only supplies needed moisture, but actually “locks moisture in” by retarding evaporation. This film also lubricates and protects the skin by

replacing the action of natural oils lost by the drying out effects of soap, water and weather. And, Alpha-Keri soothes the skin to relieve itching.

Alpha-Keri relieves the discomforts of dry, itchy skin in a wide variety of conditions including winter-itch; bath-itch; pruritus senilis; chafed or chapped skin; ichthyosis; neurodermatitis; soap dermatitis, and contact dermatitis.

Alpha-Keri is always used with water . . . added to water or rubbed into wet skin. Alpha-Keri may be added to the bath or sponged on the wet skin while showering. It is also an excellent emollient cleanser for dry hands. Available in 8 oz. bottles.

*Kerohydric® (brand of dewaxed, oil-soluble, keratin-moisturizing fraction of lanolin).

Write for samples and literature.

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measurable benefits in edema and hypertension



Before Esidrix: Pedal edema and a blood pressure of 214/110 mm. Hg.

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After Esidrix: Pedal edema cleared; blood pressure reduced to 180/94 mm. Hg. (Esidrix was given adjuactively with Singoserp and digitalis.)

plus more built-in potassium protection
than any other diuretic-antihypertensive

Esidrix-K®

50/1000 Tablets



Supplied: ESIDRIX-K 50/1000 Tablets (white, coated), each containing 50 mg. Esidrix and 1000 mg. potassium chloride (equivalent to 524 mg. potassium).

Also available: ESIDRIX-K 25/500 Tablets (off-white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. ESIDRIX Tablets, 50 mg. (yellow, scored) and 25 mg. (pink, scored).

For complete information about Esidrix and Esidrix-K (including dosage, cautions, and side effects), see current Physicians' Desk Reference or write CIBA, Summit, N. J.

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a new
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in nonhormonal
anti-inflammatory
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Geigy

Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis¹⁻⁶; gout,^{1,7,8} acute superficial thrombophlebitis^{9,10}; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)^{1,7}; severe forms of a variety of local inflammatory conditions.^{11,12,13}

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing.

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more specific than steroids—Acts directly on the inflammatory lesion without altering pituitary-adrenal function...without impairing immunity responses.^{11,14}

more dependably absorbed than enzymes—Tandearil, a simple, non-protein molecule, is rapidly and completely absorbed,^{4,15} consistently providing effective blood levels.

far more potent than salicylates—
Anti-inflammatory potency of Tandearil markedly superior to aspirin.^{2,15}

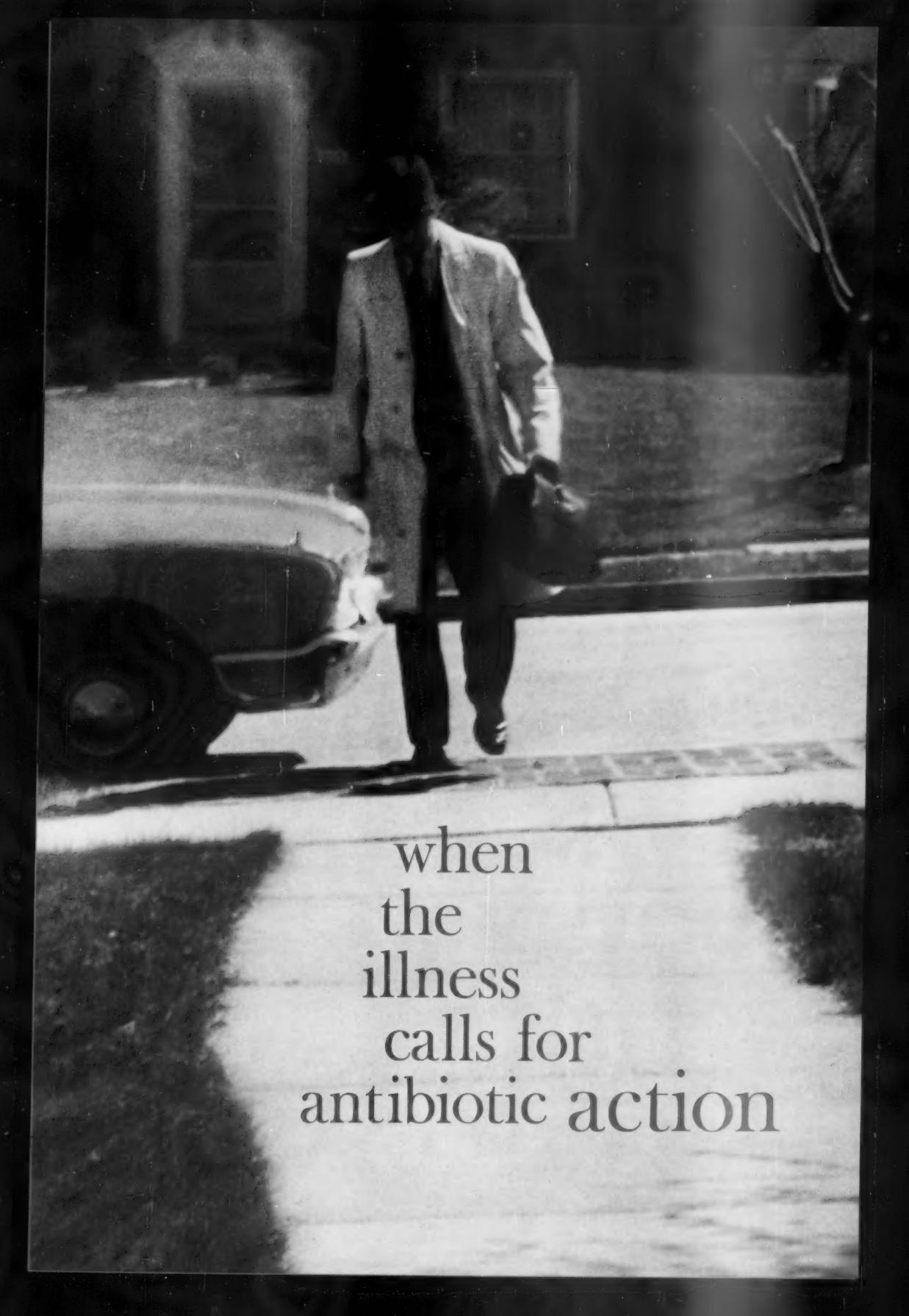
availability:

Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

references:

1. Graham, W.: Canad. M. A. J. **82**:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Kiern, I. M.: Arth. and Rheumat. **2**:212, 1959. 3. O'Reilly, T. J.: J. Irish M. A. **46**:106, 1960. 4. Cardoe, N.: Ann. Rheumat. Dis. **18**:244, 1959. 5. Robichaux, E.: General Practice **24**:14, 1961. 6. Brooke, J. W.: Western Med. **2**:81, 1961. 7. Connell, J. F., Jr., and Roussetot, L. M.: Am. J. Surg. **98**:31, 1959. 8. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 9. Stein, I. D.: Ann. N. Y. Acad. Sc. **66**:307 (March 30) 1960. 10. Barczyk, W., and Röth, W.: Praxis **49**:589, 1960. 11. Miller, J. M., et al.: Antibiotic Med. and Clin. Therap. **7**:109, 1960. 12. Connell, J. F., Jr., and Roussetot, L. M.: Am. J. Surg. **97**:429, 1959. 13. Summary of individual case histories submitted to Geigy. 14. Domenjoz, R.: Ann. N. Y. Acad. Sc. **86**:263, 1960. 15. Smyth, C. J.: Ann. N. Y. Acad. Sc. **86**:292, 1960. 16. Yü, T. F., et al.: J. Pharmacol. and Exper. Therap. **123**:63, 1958.



when
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Cherry flavor—300,000 units per 5 cc. teaspoonful, bottles of 2 fl. oz.

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For further information on limitations, administration, and prescribing of BICILLIN, see descriptive literature or current Direction Circular.
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CALLS FOR
PROLONGED
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BICILLIN®

Long-Acting

Benzathine Penicillin G, Wyeth

effective treatment of many upper respiratory infections

- produces blood levels lethal to most pathogens common in upper respiratory infections—streptococci, pneumococci, and penicillin-susceptible staphylococci
- produces prolonged blood levels, thus tending to prevent reinfection, relapse, or early recurrence
- eliminates streptococcus "carrier" state
- requires few injections . . . less trauma to patients
- affords TUBEX advantages—asepsis, less patient discomfort and ready-to-use convenience

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FOR PROMPT,
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Liquid: Penicillin V Potassium for Oral Solution, Wyeth

Tablets: Penicillin V Potassium, Wyeth

produces high penicillin blood levels

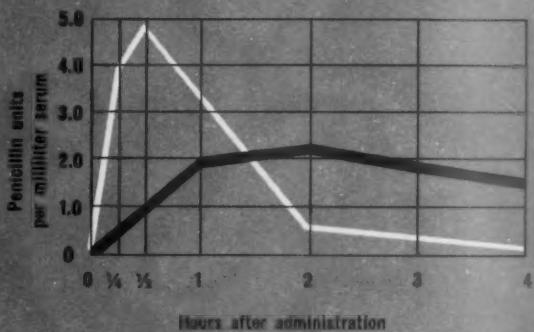
- easy-to-take Tablets or Liquid
- readily absorbed from the GI tract
- avoids pain, bother, and risk of injections
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- for all infections responsive to oral penicillin
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A potent oral penicillin for high therapeutic efficacy

You can prescribe PEN-VEE K for any and all infections caused by penicillin-susceptible organisms. It is a reliable and predictable antibiotic. Demonstrable blood levels occur within 15 minutes after ingestion: peak blood levels within 30 minutes. PEN-VEE K is markedly effective for treatment and prophylaxis of common bacterial infections, including hemolytic streptococcal infections, certain staphylococcal infections, and pneumococcal and gonococcal infections.

Serum concentrations— oral and parenteral penicillin



○ Potassium penicillin V, 250 mg. (400,000 units)—one tablet. Average of 40 fasting subjects.¹

■ Procaine penicillin G (600,000 units)—one injection. Average of 10 subjects.²

Palatable, convenient, well tolerated

PEN-VEE K is palatable, convenient (tablet or liquid), and well tolerated. These factors encourage good patient cooperation, which helps promote rapid recovery.

References: 1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-58, Medical Encyclopedia, Inc., p. 1004. 2. White, A.C., et al.: Antibiotics Annual 1955-56, Medical Encyclopedia, Inc., p. 490.

For further information on limitations, administration, and prescribing of PEN-VEE K, see descriptive literature or current Direction Circular.

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Cross section of body.
X-rays passing through
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X-ray examination simple and rapid;
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visualization always satisfactory
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How Supplied. Tablets of 500 mg., envelopes of 6 tablets, boxes of 5 and 25 envelopes, also bottles of 500.

1. Whitehouse, W. M.: Iopanoic acid, Ann. New York Acad. Sc. 78:809, July 2, 1959. 2. Baker, H. L., Jr., and Hodgson, J. R.: Further studies on the accuracy of oral cholecystography, Radiology 74:239, Feb. 1960.

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Not objectively, as intraocular pressure can be measured with a tonometer. The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

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See page 91 for description, indications, dosage, precautions, side effects, and how supplied.

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**1962—Philadelphia, Pa.,
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Controls food craving, keeps the reducer happy—In obesity, "our drug of choice has been methedrine . . . because it produces the same central effect with about one-half the dose required with plain amphetamine, because the effect is more prolonged, and because undesirable peripheral effects are significantly minimized or entirely absent." Douglas, H. S.: West.J.Surg. 59:238 (May) 1951.

'METHEDRINE'[®]

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Supplied: Tablets 5 mg., scored. Bottles of 100 and 1000.



Literature available on request.

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TABLETS
QUINIDINE
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0.1 GRAM

The Dictionary defines a cornerstone as something of fundamental importance, just as Pil. Digitalis, (Davies, Rose) and Tablets Quinidine Sulfate Natural (Davies, Rose) are of fundamental importance in treating your cardiac patients. These preparations represent 60 years of experience and dependability in the manufacture of pharmaceuticals.

Pil. Digitalis (Davies, Rose), 0.1 Gram (approx. $1\frac{1}{2}$ grains) which comprise the entire properties of the leaf, provide a dependable and effective means of digitalizing the cardiac patient, and of maintaining the necessary saturation.

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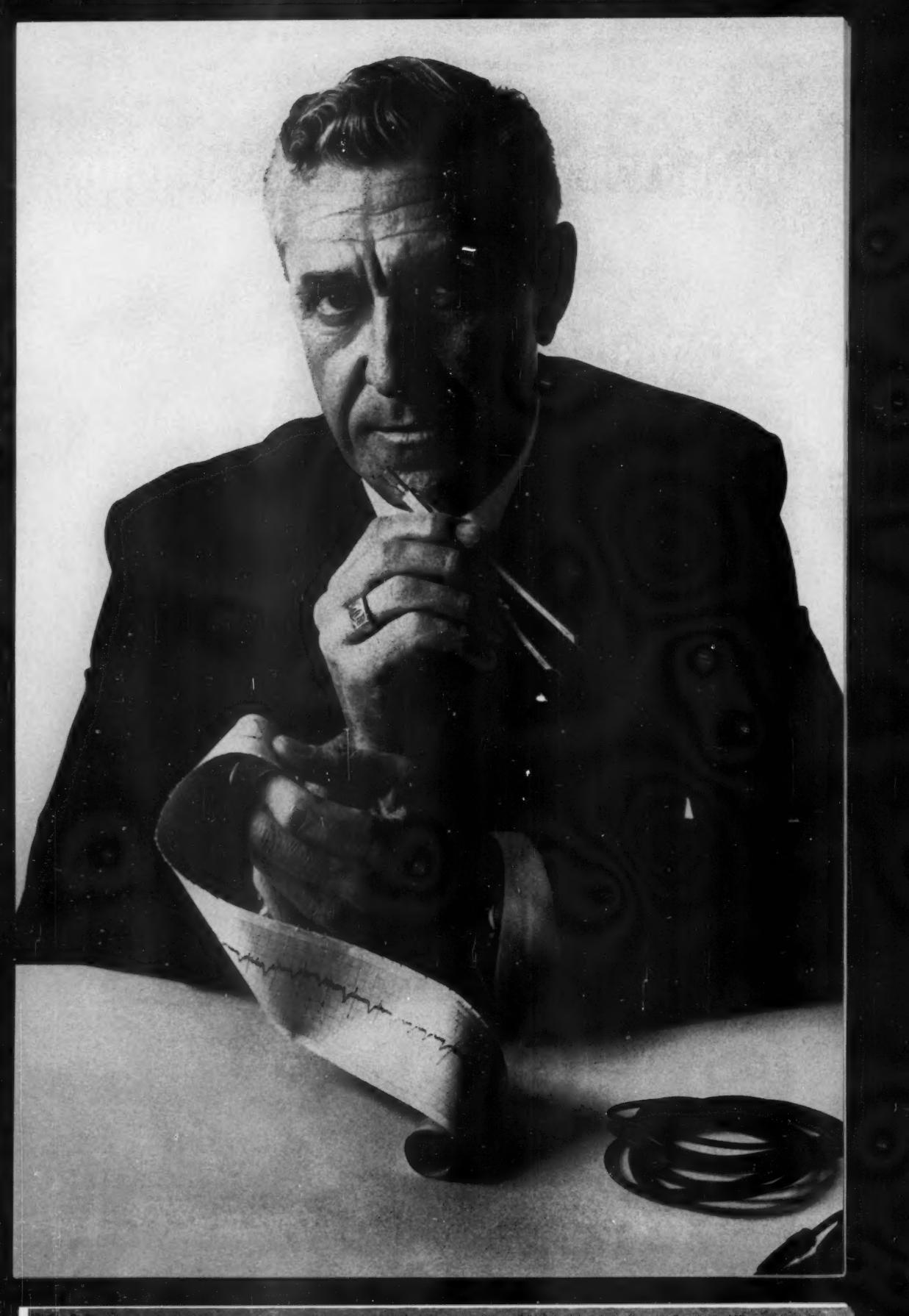
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1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.



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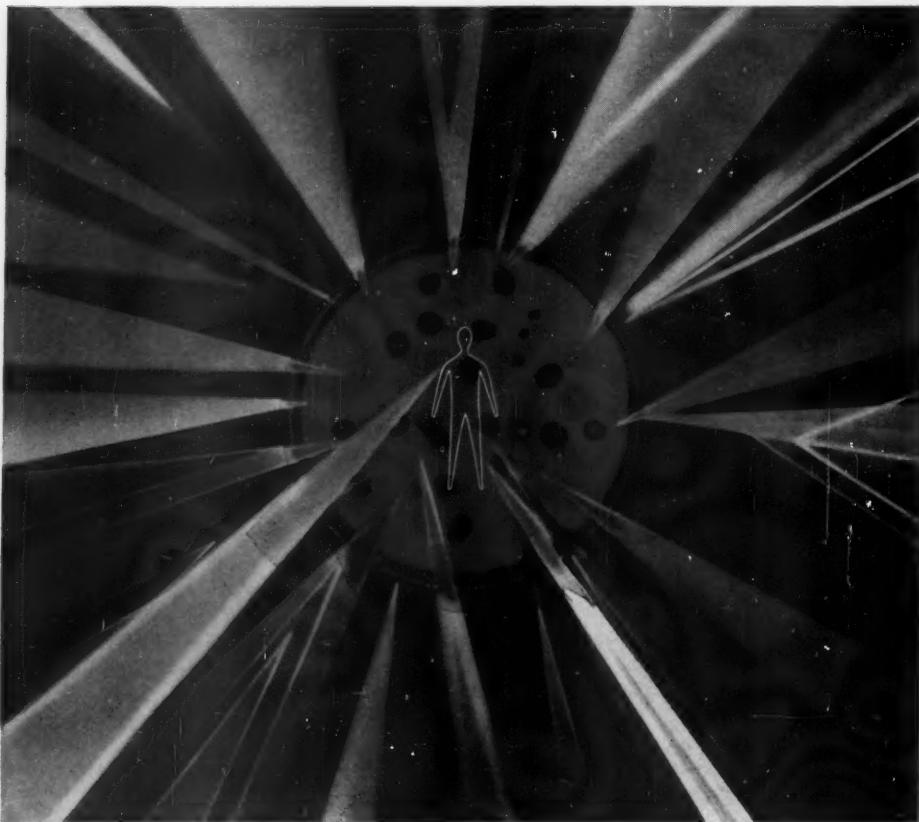


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The Role of 5-Fluorouracil in Malignant Disease

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THE UTILIZATION OF PYRIMIDINES in the synthesis of nucleic acids has resulted in investigation of their chemical analogs in the chemotherapy of advanced malignancies. A trial of fluorinated pyrimidines in animal tumors was based on the profound biological effect obtained by other compounds when hydrogen was substituted by fluorine. The most potent fluorinated pyrimidine was 5-fluorouracil [Figure 1] (1). Clinical trials in metastatic human cancers have demonstrated objective improvements in a variety of tumors (2-21). The present report is a further evaluation of this agent in an attempt to establish the role of 5-fluorouracil in cancer therapy.

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BIOCHEMISTRY OF 5-FLUOROURACIL

The rationale for the investigation of 5-fluorouracil was based on the observation that uracil was utilized preferentially for nucleic acid biosynthesis in some tumors (22). In the normal rat, exogenous preformed uracil-2-C¹⁴ was incorporated to an insignificant extent into liver nucleic acids. A much higher incorporation occurred in rat hepatomas induced chemically by acetylaminofluorene and in preneoplastic liver of animals treated with this carcinogen. In transplanted tumors (23) and rapidly growing tissues, such as intestinal mucosa (24) and regenerating liver (25), incorporation of uracil-2-C¹⁴ in the biosynthesis of nucleic acids was comparable to that of the primary hepatoma.

Subsequently, a number of uracil analogs have been studied with regard to inhibition of cell or tumor growth. Because of the profound biological effects when fluorine is substituted for hydrogen, it was considered that a fluorine substituted uracil might have tumor inhibitory activity (1). When uracil is methylated at the "5" position, thymine is formed. This position of uracil was chosen for substitution by fluorine, because it was anticipated that this analog

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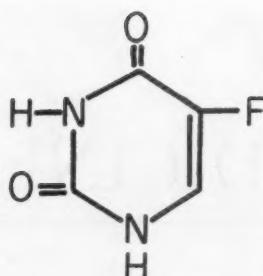


FIGURE 1. Structure of 5-fluorouracil.

(5-fluorouracil) might interfere with the formation or utilization of thymine (23). It was then demonstrated that 5-fluorouracil inhibited conversion of C^{14} -labeled formate into the methyl group of thymine (1, 26). The drug or its metabolites inhibited thymidilate synthetase, preventing the conversion of deoxyuridylic to thymidylic acids (27). In effect, 5-fluorouracil created a thymine deficiency, thereby inhibiting the synthesis of deoxyribonucleic acid (DNA). It interferes further with utilization of uracil in ribonucleic acid synthesis (RNA) by inhibiting uracil riboside phosphorylase in the pathway of formation of uridine 5-phosphate (28).

Capable of inhibiting a wide variety of animal malignant growths, 5-fluorouracil also inhibited liver regeneration, fetal growth and survival, testosterone stimulated growth of the seminal vesicle in the castrated rat, and growth hormone induced growth of the epiphyseal cartilage (29).

Study of the excretion and metabolism of 5-fluorouracil-2- C^{14} revealed that it was incorporated into ribonucleic acid (30). After a single intravenous dose, the blood radioactivity dropped quickly for the first two hours, and thereafter decreased gradually over 24 hours. One-third of the radio-carbon in the blood at one hour was due to unchanged 5-fluorouracil. Unchanged drug was present only in urine voided soon after drug treatment. No unchanged drug was detectable in the urine after three and one-half hours. The total urinary excretion

of C^{14} accumulated in 48 hours was 19.8%; of this 84% was of radioactive metabolic degradation products. These were characterized as alpha-fluoro-beta-ureidopropionic acid (FUPA) and urea (31). Conversion to respiratory carbon dioxide was 75% in 24 hours. The incorporation of labeled 5-fluorouracil into a cancer was observed in a patient given the drug four hours before surgery (30). The tumor and normal intestinal mucosa showed the greatest concentration of C^{14} , greater than the liver, and considerably greater than all other tissue samples.

REVIEW OF CLINICAL STUDIES

Preliminary clinical studies established the toxicity of 5-fluorouracil in humans (32, 33). Doses less than 8 mg per kg of body weight per day for five to eight days usually failed to produce significant clinical toxicity. Extended studies demonstrated objective evidence of tumor regression in a wide variety of tumors only in those patients manifesting severe toxic reactions (2). Of 53 patients receiving less than 15 mg per kg for five days, there was only one regression. Of 54 patients treated with more than 15 mg per kg for five days or more, 35 developed signs of toxicity, and of those, nine had objective regressions. In those not developing toxicity there were no regressions (2). One pharmacologic study failed to find a suitable dosage schedule by which one might inhibit tumor growth in man with minimal toxicity (4). Of 128 patients treated there were only eight transient regressions. It was considered unlikely that 5-fluorouracil would contribute significantly to the therapy of cancer patients. In another series of 42 patients with 11 responses (two to ten weeks in duration), it was concluded that the practical application of this therapy would be sharply curtailed because of the severe toxic effects at therapeutic dosage levels; treatment would be restricted to carefully selected cases (3, 7).

It became apparent, however, that 5-fluorouracil did have beneficial anti-tumor effects, though in order to attain objective regressions a sublethal dose must be administered leading to definite signs of toxicity (5). Further experience led to a recommended dosage schedule of 15 mg per kg per day for five days, then 7.5 mg per kg per day every other day until the first sign of clinical toxicity occurred (usually stomatitis or diarrhea). More careful selection of patients to be treated was defined (6, 9). Accumulated clinical studies have recorded objective tumor regressions primarily in cancers of the breast, ovary, large bowel, and rectum, and hepatomas (2-21).

METHOD

5 Fluorouracil was administered to 118 patients with advanced malignant disease of varied types: breast, 43; colon, 12; ovary, 8; stomach, 7; kidney, 7; advanced lymphoma, 7; melanoma, 4; neuroblastoma, 4; lung, 2; bladder, 2; myeloid leukemia, 2; various sarcomas, 6; metastatic carcinomas with an unknown primary, 5; and one each of the uterus, parotid, cervix, testis, adrenal cortex, carcinoid, nasopharynx, gallbladder, and pancreas. Terminal patients were not treated because of the reported poor tolerance to toxic effects. All patients were admitted to the Masonic Memorial Cancer Hospital of the University of Minnesota Hospitals for a period of two to four weeks for the initial course of therapy. Subsequently, monthly courses were administered in the clinic whenever possible.

All patients treated had active progressive cancer. Every patient had lesions that were measurable by clinical, laboratory, or roentgenographic methods. Evaluation of response was based entirely on objective criteria which included decrease in size or disappearance of palpable or visible masses, decrease in size or disappearance of pulmonary lesions, and recalcification of osseous lesions. Subjective improvement was not regarded as significant.

Drug Administration: 5-Fluorouracil was available in 10 ml ampules of 500 mg. It was injected undiluted, intravenously in a single dose daily, and no precautions regarding handling were necessary. The daily dose was calculated according to the patient's body weight in kilograms. If the actual weight exceeded the ideal one, the latter was used.

TABLE I. Toxic Reactions of 5-Fluorouracil

Effect	Number of Patients Recorded	Positive Reaction	Incidence (%)
Nausea, vomiting	77	47	61
Stomatitis	104	75	72
Diarrhea	73	48	65
Skin rash	69	9	13
Alopecia	84	48	57
Leukopenia (100-4,000)	109	95	87
Thrombocytopenia (only 2 <50,000)	54	45	83
Drug toxicity deaths	118	7	6

Five daily injections of 15 mg per kg of body weight were given intravenously, and a dose of 7.5 mg per kg was given every two days thereafter until evidence of toxicity appeared. As the investigation proceeded the dose was limited to a maximum of five doses even though no toxicity had appeared, and a single dose daily never exceeded 1 g. Therapy was stopped whenever the earliest signs of toxicity were apparent. Subsequent courses consisting of one or two fewer injections than given in the initial course were administered at periods of four to six weeks.

In patients who had received previous irradiation therapy or alkylating agents, or with extensive tumor involvement of the bone marrow, the dosage schedule was modified by giving fewer or smaller injections. If this was tolerated, subsequent courses were increased in amount until mild toxicity occurred.

RESULTS

TOXIC EFFECTS

The incidence of toxic reactions to 5-fluorouracil is tabulated in Table 1. The short survival of some patients limited the number of patients for evaluation of late side effects. Tabulation of the side effects was made only when positive or negative statements were recorded.

Occasionally a feeling of warmth and a metallic taste were noted during the injection. There was no serious local irritation in a few instances of accidental infiltration

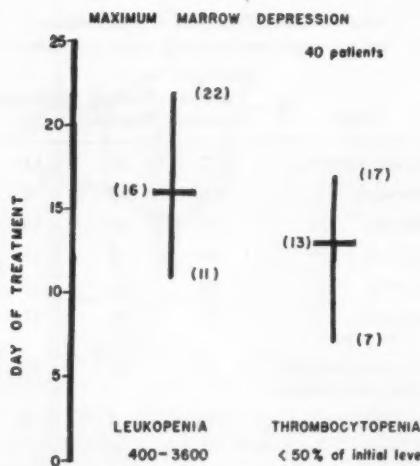


FIGURE 2. Day of maximal marrow depression after first dose of 5-fluorouracil in 40 patients intensively studied.

in the subcutaneous tissues. No phlebitis or phlebothrombosis occurred. During the days of injections and shortly afterwards anorexia, nausea, and occasionally vomiting occurred in 61% of the patients evaluated. Some patients already had such complaints due to the cancer, hence true evaluation of this effect could not be made. In a few patients pain in the tumor masses occurred shortly after injection of 5-fluorouracil.

Stomatitis (72%) was employed as one of the earliest signs of toxicity. It began as dryness of the mouth, burning of the lips, and hyperemia of the mucosa, occurring about the third to fifth day. More severe manifestations consisted of ulcerations of the lip or mouth appearing the fifth to the tenth day after the first dose was given. The severe stomatitis was associated with difficulty in swallowing, decrease in fluid intake, and decrease in eating. Oral fluids were encouraged, and occasionally intravenous supplements administered. Severe stomatitis cleared within two weeks.

Diarrhea (65%) and abdominal cramps usually occurred after the stomatitis. The alteration of the oral mucous membrane

was characteristic of the entire gastrointestinal tract. Similar mucosal change was seen on colostomy stoma. The diarrhea consisted of frequent, small, watery stools usually controlled by paregoric. With severe mucosal damage, adynamic ileus occurred, lasting ten days in one patient. Upon recovery of function shreds of sloughed mucosal tissue were passed in the feces. The reduction of oral fluid intake due to stomatitis, profound loss of fluid by diarrhea, and loss of plasma through damaged mucosal walls resulted in occasional decrease in blood volume and hypotension requiring intravenous fluids, plasma, and whole blood.

Dermatological changes occurred in nine patients. These consisted of diffuse erythema, scaling, desquamation, or bullous formation. Later hyperpigmentation of the skin occurred. One patient with atrophy of the facial skin from old irradiation changes showed a bright erythema of the involved skin and superficial ulcerations. Nails underwent changes of increased brittleness and cracking, and an irregular ridge formed. With many courses of therapy, several such ridges were visible.

Alopecia (57%) of varying intensity occurred after the acute toxic phase. The hair became dry and brittle, and it fell out. The loss varied from thinning to complete baldness. Regrowth of hair occurred even in patients receiving repeated courses of therapy.

Hematopoietic depression was reflected in the peripheral blood in the form of leukopenia (87%), thrombocytopenia (83%), and mild anemia. Leukopenia was designated when the total white blood cell count was less than $4,000/\text{mm}^3$. Primarily a granulocytopenia, it occurred from the eleventh to the twenty-second day after the first dose of 5-fluorouracil (Figure 2). The average day of maximal leukopenia was the sixteenth day. Levels as low as 100 were recorded. The leukopenia lasted from a few to ten days; recovery was rapid. Initially cortisone was employed to stimulate leuko-

cytes, but observations demonstrated that adrenal steroids had no effect (Figure 3). The rate of onset of leukopenia and recovery remained similar with or without adrenal steroid therapy (Figure 4). Prophylactic antibiotic therapy was employed if ulcerated skin lesions were present, since these represented a site of entering infection. With white blood cell counts below $1,000/\text{mm}^3$, modified protective isolation was employed.

Thrombocytopenia (83%) occurred maximally from day seven to day 17, the average being the thirteenth day. The degree of thrombocytopenia was mild, only two patients going below 50,000. Petechiae and bleeding were rare. The rate of recovery was slower than with the white blood cell count. Mild decreases in hemoglobin occurred.

Fever occurred during the end of the second week concomitantly with leukopenia and the gastrointestinal symptoms of toxicity. In most instances blood cultures were sterile and presence of infection could not be established. Septicemia occurred in only three instances. The fever appeared to be a general toxic phenomenon, and did not respond to intensive broad-spectrum antibiotics. Hypophysectomized patients maintained on 50 milligrams of cortisone were prone to develop this fever, apparently be-

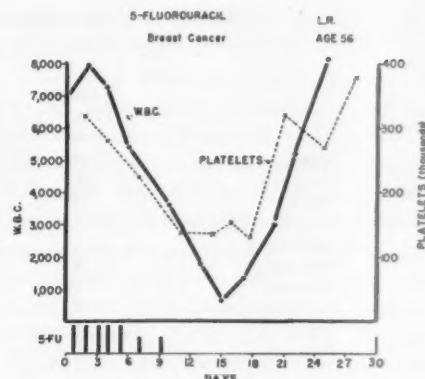


FIGURE 4. Pattern of leukopenia and thrombocytopenia following 5-fluorouracil therapy without adrenal steroid therapy.

cause of adrenal insufficiency. Increased doses of cortisone above 100 milligrams daily corrected this poor tolerance to stress.

Seven deaths occurred as the result of therapy. Two were due to profound diarrhea and shock in debilitated patients. The intestinal mucosa was destroyed throughout the bowel. Two patients had massive liver metastases. Three patients died of infection (two of septicemia, one of pneumonia). These deaths occurred during the period of maximal leukopenia. The mortality rate for the series was 6%.

The toxic reactions during therapy were of three stages: an acute phase during the end of the first week primarily with stomatitis and diarrhea; a phase of fever, leukopenia, and general toxicity during the end of the second week or beginning of the third week of therapy; and a late phase after four weeks with alopecia and skin pigmentation. The toxic reactions which the patients demonstrated were more severe in debilitated patients and those who had previous intensive irradiation therapy or other cytotoxic chemical therapy.

CLINICAL RESULTS

5-Fluorouracil was administered to 118 patients. No objective improvement was noted in 87. Definite objective improve-

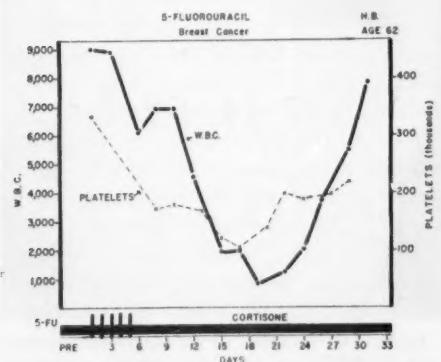


FIGURE 3. Leukopenia and thrombocytopenia occurring following therapy despite cortisone 200 mg a day.

TABLE 2. Improvements from 5-Fluorouracil—94 of 118 Patients

	Number Treated	Number Improved	Duration in Months		
			2	2-6	6
Breast	43	18	5	4	9
Colon	12	1			1
Ovary	8	2	1		1
Unknown primary	5	1			1
Lymphoma	7	1		1	
Sarcoma	6	1		1	
Stomach	7	3	3		
Neuroblastoma	4	2	2		
Testis	1	1	1		
Pancreas	1	1	1		
Total	94	31	13	6	12

ment occurred in 31 patients (26%). The type of tumor responding has been tabulated in Table 2. The most favorable group was that of breast cancer.

The improvements noted were of varying duration (Table 2). Regressions lasting less than two months occurred in 13 patients. Three patients with stomach cancer had disappearance of large masses during the period of toxic reaction. By the time the leukopenia had regressed, the tumor masses were also growing. It was apparent that tumor regressions correlated with the toxic reactions. Regressions lasting two to six months occurred in six patients. Twelve patients (10%) had improvements lasting more than six months, five of which were greater than one year. Three of the latter are still in remission.

Of the 118 patients, 107 are dead. Those patients demonstrating improvement survived longer than those who did not respond. The majority of those now alive demonstrated objective remissions. The advanced state of the disease in many patients treated is demonstrated by the fact that 23 (19.5%) died within one month, including, however, the seven recorded as deaths due to drug toxicity.

The largest homogeneous group in this series was that of breast cancer. Of 43 patients treated, 18 improved. Nine of these

had improvements lasting more than six months, four of which were greater than one year (Figures 5A, 5B). The 18 patients who improved had an average survival of

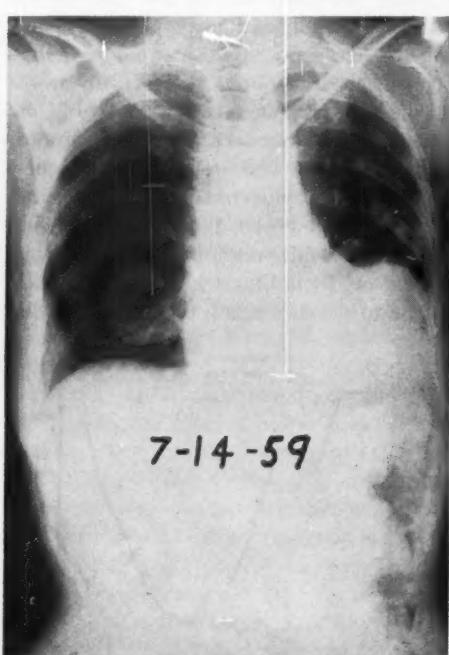


FIGURE 5A. Metastatic breast cancer with a large mass in left lower lobe and osseous metastases. Patient, age 49 years, had previously failed to respond to estrogenic and androgenic hormone therapy.

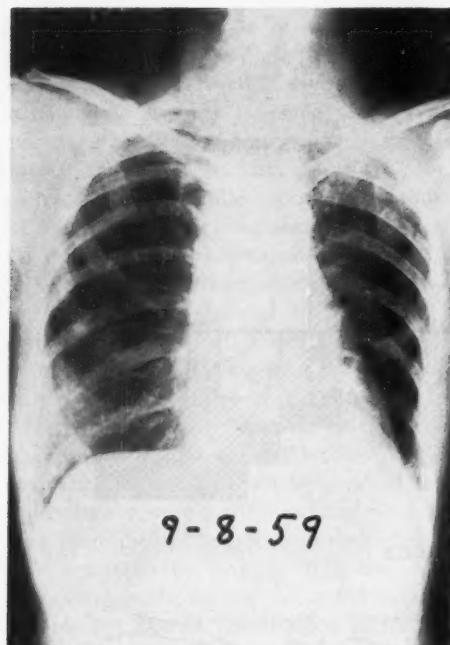


FIGURE 5B. Disappearance of tumor mass two months after 5-fluorouracil. Disease controlled for 18 months with 12 courses of drug.

ten months; seven are still alive. The patients failing to respond survived an average of three months; only one is still alive. In this breast cancer group there was no correlation between the response to 5-fluorouracil and the previous response to hormone therapy.

Biochemical Alterations: Hypercalcemia due to bone metastases decreased to normal during improvement due to 5-fluorouracil therapy. A metabolic balance study in one patient (Figure 6) demonstrated a decrease to normal of hypercalcemia and a negative calcium balance decreased to equilibrium. A positive calcium balance and recalcification of bone lesions did not occur though soft tissue masses decreased markedly in size and pain disappeared.

Measurement of circulating tumor cells in peripheral blood revealed a disappearance of cancer cells from the blood, even

though no objective improvement in the cancer was observed.

Combined Therapy: Attempts to evaluate the potentiation of irradiation therapy by 5-fluorouracil were made in four patients. No improvement occurred greater than that expected by irradiation alone. One patient with multiple skin metastases from melanoma provided an excellent controlled study. Three skin lesions were treated with irradiation alone at doses of 2,000 roentgens, 3,000, and 6,000. Though all three lesions showed improvement, the best response was with the lesion receiving 3,000 roentgens. No better improvement was noted when similar lesions were later treated in the same manner concomitantly with 5-fluorouracil.

DISCUSSION

5-Fluorouracil was developed in the basic science laboratory, intensively studied biochemically, screened through animal tumors, and brought forth for clinical evaluation in human cancers. Since early enthusiastic clinical results were reported (2, 9), 5-fluorouracil has been tested by several investigators (3-21).

It is apparent that 5-fluorouracil is able to produce objective remissions in a variety of malignant tumors. This response follows administration of a maximal or sublethal dose, and is usually associated with severe toxicity. Consistent toxic reactions from 5-fluorouracil in the usual chronological order are: nausea or vomiting, stomatitis, diarrhea, leukopenia, fever, and alopecia. The effects on the mucous membranes, the hematopoietic system, skin, and hair, represent the physiological effects of an antimetabolite blocking nucleic acid synthesis in rapidly proliferating normal tissues. Concomitant damage to tumor cells also occurs.

The tumors reported to respond best to 5-fluorouracil have been those of breast, colon, rectum, and hepatocellular carcinomas. Tumors consistently refractory to

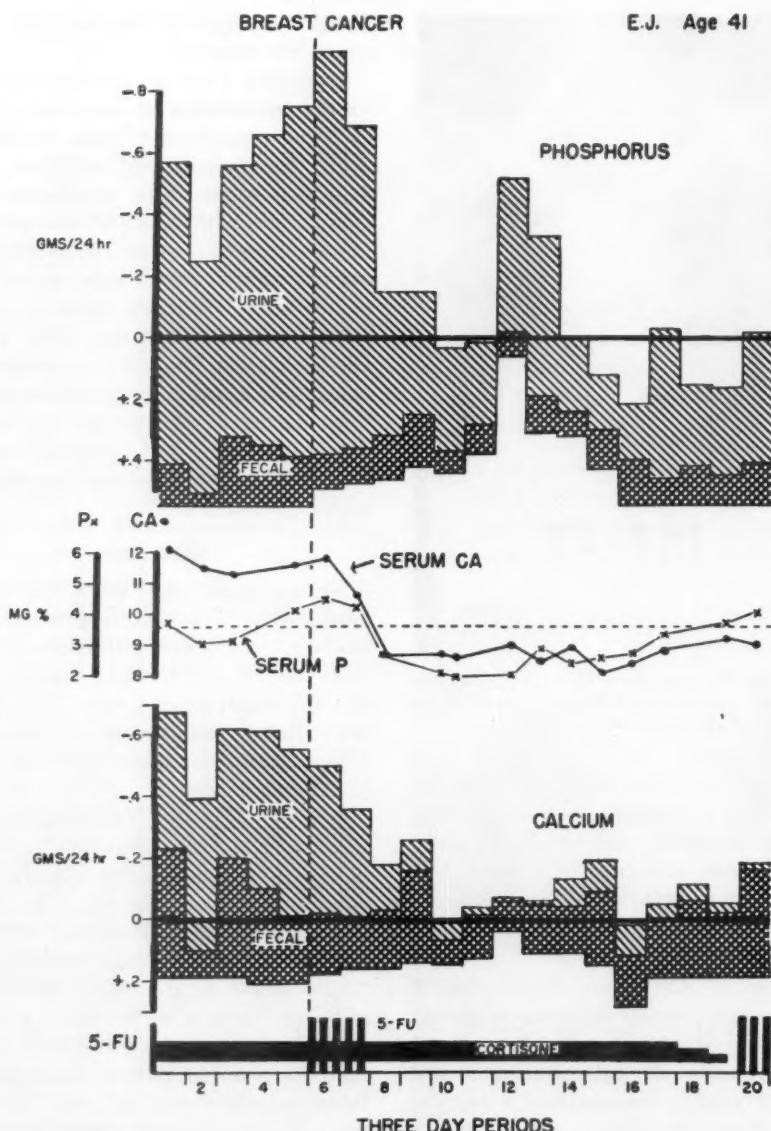


FIGURE 6. Metabolic balance study in a breast cancer patient receiving 5-fluorouracil. The disease had previously failed to respond to castration, androgenic hormone, or triethylene thiophosphoramide, but had been controlled for one year with 300 mg of cortisone daily.

this therapy include cancers of the kidney, uterus, lung, esophagus, cervix, larynx, prostate, and pancreas, melanoma, and fibrosarcomas. Other cancers demonstrating fleeting or equivocal responses are those of

the ovary, stomach, bladder, neuroblastoma, Ewing's sarcoma, and lymphoma.

Comparison of the results of the present study in the treatment of a wide variety of tumors is similar to the experiences of other

investigators. Shrinkage of tumor masses was noted in tumors of the ovary, colon, stomach, neuroblastoma, undifferentiated carcinomas, Ewing's sarcoma, and lymphoma. Significant improvements (see below) occurred in cancers of the breast, ovary, and one undifferentiated carcinoma of unknown primary. In general, the effect on colon carcinomas was unimpressive.

A significant difference in the reported data exists due to the variability of the criteria of improvement. Fleeting regressions of tumor masses during the period of toxicity from the initial therapy frequently were enthusiastically recorded as objective improvements, though seldom were these maintained more than a few weeks. These regressions were closely associated with severe toxicity, and frequently death ensued as a result of the toxicity. It is apparent that, though the tumor decreased in size, the patient cannot be classified as having sustained a significant objective improvement. It can be presumed that if other chemotherapeutic agents such as nitrogen mustard, triethylene thiophosphoramide, or cyclophosphamide were administered to the same degree of toxicity as 5-fluorouracil, regressions of the same fleeting nature would be observed. At most the value of the fleeting regression with this agent was to demonstrate that it also has antineoplastic activity.

Of 993 patients treated with 5-fluorouracil and culled from published reports (2-21), a total of 210 objective improvements (21%) was reported. The large individual studies employing comparable doses reveal a regression rate of 15 to 20% (9, 12, 15, 21). Of the 118 patients treated in the present study, 31 (26%) had objective regressions. However, only 18 (15%) were of greater than two months' duration. Of these, 12 patients (10%) maintained objective regressions more than six months. A similar regression rate for the six-month period has been recorded from 1,233 patients with breast, colon, and rectum cancers assembled

from a large group of investigators' pooled data (34). Therefore, at least 10% but not more than 20% of patients treated to date have had significant objective improvement from 5-fluorouracil therapy.

Breast carcinoma has had the best results of all the tumors treated (2, 9, 13, 15). The present report substantiates this. Advanced breast cancer has been effectively controlled by hormonal therapies in about 25 to 35% of patients. The improvements noted with hormonal therapies are superior to those noted with 5-fluorouracil. However, this agent produced objective regressions of significant duration in tumors no longer controlled by hormone therapy, or in those refractory to hormone therapy. Therefore, it provides an additional therapeutic agent for the prolonged control of advanced breast cancer.

The high degree of toxicity of 5-fluorouracil therapy has resulted in increased morbidity. Patients not demonstrating improvements as a result of the toxicity became more rapidly debilitated, and therefore survival time was decreased.

Efforts to reduce the toxicity of 5-fluorouracil have been investigated. It was administered as an eight-hour infusion for five days followed by 250 mg per day orally for 14 to 30 days. Much of the systemic toxicity for non-malignant tissues was avoided without significant impairment of the limited antitumor effects of the drug (35). Our preliminary investigations have demonstrated the decrease in toxicity by the eight-hour infusion.

Combination Therapy: Combination therapy with irradiation and 5-fluorouracil has been attempted (36-39). Irradiation was limited to a tumor dose of 2,500 roentgens in cancers of the lung, head and neck, and esophagus, ordinarily resistant to the drug. This combined therapy was reported to result consistently in tumor regression greater than that seen with irradiation alone. This was interpreted as an additive effect when both agents were used simul-

taneously, or when one agent potentiated the antitumor effect of the other (38). The study was not carried out with controls. The variability of response to irradiation makes evaluation of combined therapies difficult. In the present report, of four patients so studied, no potentiation of effect was noted. Similar difficulty in evaluating response was noted in combination of 6-mercaptopurine with 5-fluorouracil (40).

5-Fluoro-2'Deoxyuridine: Derivatives of pyrimidines similar to 5-fluorouracil have been studied in an attempt to obtain greater antitumor effect with less toxicity. The nucleoside 5-fluoro-2'deoxyuridine (FUDR) was found to be more effective and less toxic than 5-fluorouracil against transplanted animal tumors (41). Clinical studies have demonstrated tumor regression in patients with cancer of the breast, colon, stomach, and with leukemias (42-45). No therapeutic advantage of 5-fluoro-2'deoxyuridine over 5-fluorouracil was apparent. The high cost and small supply of the compound have limited extensive studies (43).

RECOMMENDATIONS

The experiences of the present study and of other investigators provide criteria for selection of patients for 5-fluorouracil therapy: The patient must be in relatively good nutrition without profound debilitation; extensive irradiation therapy should not have been given; recent or large doses of cytotoxic chemotherapy should not have been administered; extensive hepatic metastases or marked impairment of liver function should not be present; the bone marrow function must be adequate; no major surgical procedure should have been done within the past 30 days; and no known existing infections should be present. The anticipated reactions to 5-fluorouracil should be thoroughly explained to the patient.

The patient is hospitalized during the first course of therapy to determine the dosage that produces minimal toxicity. Se-

vere reactions during the initial course of therapy can be managed more effectively in the hospital. The dose is based on the patient's actual weight or ideal weight, if obese. The drug is administered daily at a dose of 15 mg per kg until the first sign of toxicity occurs, but not to exceed five days. The daily dose should not exceed 1 gram.

Adequate fluid intake must be maintained. If severe diarrhea occurs, intravenous fluids, plasma, and whole blood are given. If leukopenia less than 1,000 develops, protective isolation and antibiotics are employed, preferably by mouth. Patients with ulcerated cutaneous tumor lesions are placed on prophylactic antibiotic therapy before the onset of leukopenia. Cortisone therapy is not used in the management of leukopenia.

Because of the action as an antimetabolite, repeated courses of 5-fluorouracil are administered every four weeks, though this can be done on an ambulatory basis. The dose is one or two injections fewer than are required to produce minimal early toxic signs during the initial course.

SUMMARY

The drug 5-fluorouracil is an antimetabolite with antineoplastic properties. Objective tumor regressions of greater than six months have occurred in 12 (10%) of 118 patients. The antitumor effect is closely associated with the development of severe toxic reactions including stomatitis, diarrhea, leukopenia, and alopecia. It appears that 5-fluorouracil is most effective in breast cancer. This therapy has a limited role in the treatment of selected patients with advanced breast cancer not responsive to hormonal therapy.

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Memorial Hospital for their intensive supportive care of the patients.

SUMMARIO IN INTERLINGUA

A causa del facto que le pyrimidina "5-fluorouracil" interfere in le formation o in le utilisation de thymina, un essayage de su proprietates antineoplastic esseva interprendite. Le composito esseva administrate a 118 patientes. Un definite melioration objective occurreva in 31 (26%). Tamen, solmente 18 del regressiones objective (15% del serie total) habeva duraciones de plus que duo menses. De iste 18 patientes, 12 (10% del total) manteneva regresiones objective durante plus que sex menses. Esseva apparente que 5-fluorouracil esseva le plus efficace in cancre mammari. Meliorationes etiam occurreva in canceres del ovarios e in non-differentiate carcinomas. Meliorationes objective in cancre del colon—per contrasto con le reportos de altere investigatores—non esseva observate.

Le responsas objective notate occurreva post le administration de maximal dosages subletal de 5-fluorouracil. Usualmente illos esseva associate con grados sever de toxicitate. Le reactiones toxic que esseva evocate constantemente per 5-fluorouracil esseva nausea o vomito, stomatitis, diarrhea, leucopenia, febre, e alopecia. Un mortalitate de 6% esseva notate como efecto del therapia. Le alte grado de toxicitate del therapia a 5-fluorouracil ha resultate in un augmento del morbiditate. Le patientes qui non respondeva per ulle melioration se debilitava plus rapidemente in consequentia del toxicitate drogal, e le duration de lor superviventia esseva reducite.

Esseva concludite que 5-fluorouracil ha un rolo restringite in le tractamento de seligite patientes con aviantate cancre mammari que non responde al therapia hormonal.

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An Evaluation of 5-Fluorouracil in Malignant Disease

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UNTIL RECENTLY, it was believed that preformed pyrimidines, unlike preformed purines, were not utilized by mammalian tissues, either normal or neoplastic. In 1954, Rutman, Cantarow, and Paschkis (1) observed that uracil was incorporated into preneoplastic rat liver and rat hepatoma. In 1957, Heidelberger, Leibman, Harbers, and Bhargava (2) verified this finding and noted that significant incorporation of uracil occurred into intestinal mucosa and several carcinomas of mice and rats. Because of these findings, many pyrimidine antagonists have been synthesized and evaluated for their effect in malignant disease. Of these drugs, 5-fluorouracil (3), 5-fluorodeoxyuridine (4), and 6-azauridine (5) have been subjected to fairly extensive trial. 6-Azauridine has, up to now, shown only a transient effect upon leukemias and solid tumors (6). Drugs 5-fluorouracil and 5-fluorodeoxyuridine have been studied extensively in the past three years and both have shown effects in several types of solid tumors that had previously been relatively resistant to the other available chemotherapeutic agents. Both agents are quite toxic, and controversy exists at the present time as to the value of these compounds in the therapy of malignant disease (7, 8). Between January 1959 and October 1960, members of the Cancer Chemotherapy Group at Jefferson Medical College treated 163 patients having disseminated malignancy with

5-fluorouracil. Adequate follow-up was available in 149 of these patients. This report summarizes our findings with this drug.

MECHANISM OF ACTION

Figure 1 illustrates the chemical structure of 5-fluorouracil and its relationship to uracil and thymine. The fluorine atom is small and tightly bound to the pyrimidine ring. Consequently, 5-fluorouracil follows the pathways of uracil in intermediary metabolism and prevents the conversion of uracil to thymine (9). Figure 2 demonstrates current concepts of the formation of ribonucleic acid and desoxyribonucleic acid outlining the sites of demonstrated 5-fluorouracil block (9-18). Of these, the irreversible inhibition of the enzyme, thymidylate synthetase, by a metabolite of 5-fluorouracil, 5-fluorodeoxyuridylic acid, is believed to be most important for anti-tumor effect (17).

The pharmacology of the fluorinated pyrimidines has been intensively studied by Heidelberger, Ghobar, Baker, Mukherjee, Kaldor, and Danneberg (19, 20). 5-Fluorouracil is rapidly metabolized, the major catabolic site being the liver. All tissues are capable of degrading the drug although tumor tissue appears selectively deficient in this function (21), possibly because of its relative deficiency in catabolic nucleic acid enzymes (21-23). 5-Fluorouracil is degraded to fluorouridopropionic acid, urea, and carbon dioxide, and a significant percentage is excreted in the urine intact. The drug is rapidly metabolized, 75% or more disappearing from the body within 24

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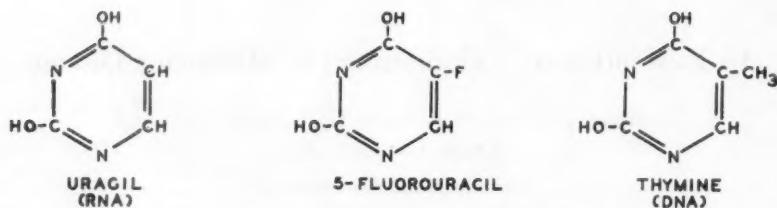


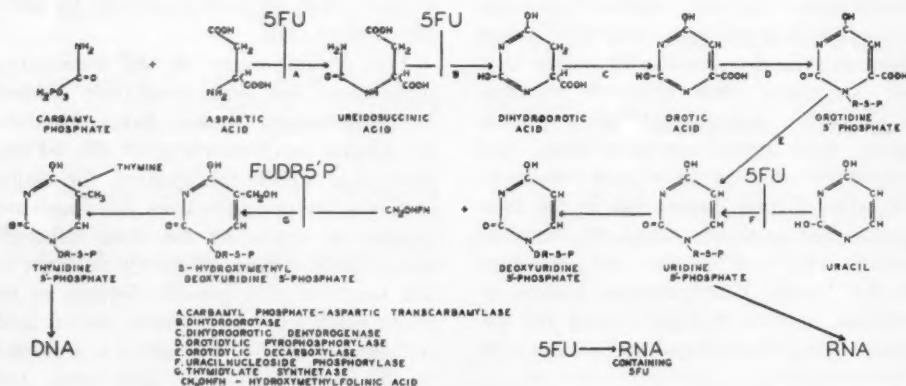
FIGURE 1. The chemical structure of 5-fluorouracil and its relationship to uracil and thymine.

hours (24). These basic findings may help explain some of the effects of the drug in patients. Thus individuals depleted in protein and those undergoing recent surgery have been found to develop toxicity with a dosage significantly lower than the average patient can tolerate (25). This may be due to interference with ribonucleic acid formation and consequent interference in new protein formation. A high protein intake has been found to decrease toxicity of the drug (25). The major role played by the liver in detoxification of the drug suggests that individuals with significant hepatic disease would be quite sensitive to 5-fluorouracil. This has been found true in practice. In tissue cultures and bacterial systems, thymidine has been found effective in

reversing 5-fluorouracil toxicity. However, in *in vivo* experiments in animals, neither thymidine, thymine, nor uracil has had any effect on drug toxicity if given 24 hours or more after 5-fluorouracil (26).

SELECTION OF PATIENTS

Only those patients with obviously incurable cancer who were believed to be refractory to standard modalities of treatment were selected for study. No patient who was leukopenic, thrombocytopenic, or whose bone marrow was significantly hypoplastic was treated. Irradiation of large areas of bone marrow or use of alkylating agents or other marrow suppressive drugs was a deterrent to treatment, and no patient was started unless his peripheral blood



BIOSYNTHESIS OF PYRIMIDINE NUCLEOTIDES

FIGURE 2. Current concepts of the formation of ribonucleic acid and deoxyribonucleic acid outlining the sites of demonstrated 5-fluorouracil block.

and bone marrow had returned essentially to normal. Early in our experience, we found that recent major surgery greatly increased the toxicity of the drug. Present policy is not to use 5-fluorouracil, if at all possible, until relatively normal eating habits have been resumed. If it is necessary to give the drug in the early postoperative period, a high protein intake, if necessary by such means as tube feeding, is prescribed for several days prior to and during therapy. Cachexia due to disseminated cancer or extensive hepatic metastasis was found by ourselves as well as others to be associated with severe toxicity (3). Here again, protein was forced, and reduced doses of the drug were used.

REGULATION OF DOSAGE AND TOXICITY

Our dosage regimen followed that recommended by Curreri, Ansfield, McIver, Waisman, and Heidelberger (3), and consisted of 15 mg/kg for five days in individuals who were well nourished, had not had recent major surgery, and whose clinical condition did not suggest extensive hepatic metastasis. Following the initial course, the patient was not given the drug for three to four days. Until the first sign of toxicity occurred, 7.5 to 10 mg/kg were then given every other day. If the patient was malnourished, had had relatively recent surgery, or was exposed to large amounts of X ray or marrow suppressive drugs, the dosage of 5-fluorouracil was proportionately reduced. In general, the extent of the reduction depends upon clinical evaluation of the condition of the patient. Usually, we again followed the recommendations of Curreri et al. (3) and gave between 50 and 60 mg/kg within a four-day period followed by a three-day rest. If no evidence of toxicity occurred, we gave 7.5 mg/kg every other day until the first signs of toxicity were seen. Almost invariably these were found in the mouth or the gastrointestinal tract. Stomatitis with erythema or ulceration at the margin of the skin and the mu-

cous membrane was the most common initial sign. Occasionally, a diffuse soreness and erythema of the mouth occurred first. Diarrhea (by definition, the passage of more than two bowel movements a day) was also considered an indication for the cessation of therapy. It was found important to stop therapy with the first evidence of gastrointestinal toxicity. Otherwise, gastrointestinal and hematologic toxicity were liable to be severe. Review of our data suggested that the type of toxicity was related to the intensity of early treatment. Severe stomatitis appeared to be more common in those who received large doses over a short time, whereas diarrhea appeared to be the rule in those who were given small doses over a longer period. Usually within four days of the first evidence of gastrointestinal toxicity, laboratory evidence of depression of bone marrow function occurred. The initial disturbance consisted of a moderate to severe fall in peripheral white and platelet counts. Occasionally, despite the use of standard doses of the drug, white blood counts of under 1,000/mm³ were found. Thrombocytopenia was the rule, and a platelet count in the neighborhood of 50,000/mm³ was not unusual. Generalized bleeding, however, was not seen. Considering the depression in white blood count, infection was not common, and our policy was not to use antibiotics prophylactically. When infection occurred the most common manifestation was septicemia, the organisms appearing to enter through the gastrointestinal tract. The most common infecting organisms were *Pseudomonas pyocyanea*, *Bacillus proteus*, and *Escherichia coli*. Vaitkevicius (27) recommends the use of oral neomycin during the leukopenic phase; in view of our experience this seems to be a logical procedure, especially in individuals with lesions involving the gastrointestinal tract or the liver. Other toxic manifestations were not too common and were not life-threatening. An unusual side effect that had not been reported before

TABLE 1. Toxicity of 5-Fluorouracil in 144 Patients

	without Liver Disease Patients 108	with Liver Disease Patients 41	Performance Status Greater than 60 70 Patients	Performance Status 60 or Less 79 Patients	Total Number of Patients with Symptom	Percentage of Patients with Symptom
Nausea	18	6	12	12	24	16%
Stomatitis	56	30	43	44	87	58%
Diarrhea	65	31	45	51	96	64%
Moderate leukopenia $3,000/\text{mm}^3$ to $4,500/\text{mm}^3$	69	32	47	54	101	69%
Severe leukopenia less than $3,000/\text{mm}^3$	24	16	16	24	40	27%
Moderate thrombocytopenia $80,000/\text{mm}^3$ to $150,000/\text{mm}^3$	74	27	53	48	101	70%
Severe thrombocytopenia less than $80,000/\text{mm}^3$	24	15	21	18	39	27%
Significant alopecia	5	2	4	3	7	5%
Dermatitis	7	3	5	5	10	7%
Death	3	5	2	5	8	6%

was an optic neuritis seen twice in one patient. Whether or not this was due to the drug we do not know; however, both times it coincided with therapy. No suggestion of optic damage was seen in any other patient in this series. A scaling skin was not uncommon, but it rarely caused discomfort or required therapy. Seven patients died probably directly from the use of the drug. The major cause of death was septicemia, but electrolytic imbalance contributed to the death of two patients. Table 1 tabulates the toxicity found in this series of patients.

CLASSIFICATION OF RESULTS

Results are tabulated in Table 2. We have classified our responses as objective remissions, subjective remissions, and failures. To qualify as having an objective remission, a patient must have had significant reduction in the size of the major measurable tumor mass for a period of six weeks or more. An improvement in performance status with associated subjective improvement must also have occurred. If

more than one mass was measurable, the largest mass was used for classification. Whenever possible, masses were used that could be directly measured, such as pulmonary metastases. A significant increase in the size of any mass prevented a response from being classified as an objective remission. If no mass could be observed, the following were used as evidence of objective remission: (a) persistent relief from chronic intestinal obstruction, and (b) significant reduction in serum bilirubin in those patients with biliary tract obstruction due to tumor. Cessation of bleeding or discharge from a tumor was not considered evidence of objective response. Subjective responses included those individuals who had measurable masses that did not objectively regress although their performance status and general well-being did improve for a minimal period of six weeks. It must be realized that a certain percentage of the patients treated did not have easily measurable tumor masses. Therefore, the maximal response possible would be a subjective one. Length of remissions was also

classified as short (from six weeks to three months) or protracted (over three months). In agreement with other investigators, our remissions were usually short-lived, especially in those patients with gastrointestinal lesions. Because of this, we have been treating patients again at intervals varying between eight and ten weeks. Originally, we tried to treat at shorter intervals, but severe toxicity commonly ensued and, therefore, less drug could be given to the patients during the second course.

CARCINOMA OF THE GASTROINTESTINAL TRACT AND RELATED ORGANS

Carcinoma of the gastrointestinal tract and related organs has been discussed in a previous paper (28). Approximately 25% of those with carcinoma of the gastrointestinal tract had some significant response. While most of the patients treated had

carcinoma of the rectum or colon, significant responses were seen in hepatomas, carcinomas of the stomach, and in one patient with carcinoma of the pancreas. Symptoms commonly relieved included those of intestinal obstruction, bleeding, and deep abdominal pain. Two patients had relief of severe anorexia and jaundice due to hepatic disease, a response believed to be rare by other observers. Almost invariably symptomatic relief was short, and treatment again was required within a two-month period. Satisfactory response from a second course of therapy was not unusual although repeated courses commonly produced lessened degree and duration of response. Two of these patients had concomitant radiotherapy and 5-fluorouracil with the hope of prolonging the duration of remission; both had remissions that lasted less than three months.

TABLE 2. Response of Various Tumors to 5-Fluorouracil

Site	Number	Number with Objective Response	Number with Subjective Response Only	Number with Remissions Lasting 6 to 13 Weeks	Number with Remissions Lasting Longer than 13 Weeks
Colon	37	10(27%)	7(19%)	10	3
Stomach	10	4*	3	3*	1
Pancreas	5	1	1	2	0
Liver and biliary tract	5	2*	0	2*	
Breast	38	15(39%)	8(21%)	16	7
Lung	10	0	2	2	0
Bladder	6	0	1	1	0
Ovary	4	2	0	1	1
Prostate	4	1	0	1	0
Soft tissue sarcoma	3	0	0	0	0
Endometrium	3	1	1	1	1
Larynx	3	1	0	1	0
Adenocarcinoma site unknown	2	0	1	1	0
Cervix	2	0	1	1	0
Osteosarcoma	2	1*	0	0	1*
Testicular tumor	2	0	0	0	0
Hypernephroma	2	0	1	0	1
Thyroid	2	0	0	0	0
Lymphoma	2	0	0	0	0
Melanoma	1	0	0	0	0
Leukemia (acute lymphatic)	1	0	0	0	0

* One patient received concomitant radiotherapy.

CARCINOMA OF THE BREAST

Significant regressions were seen in a relatively high percentage of 38 patients with carcinoma of the breast treated in this series. We could find no correlation between the response and the cell type. Significant remissions were seen in this series in three persons who had proven to be completely refractory to alkylating agents, and in two patients whose lesions appeared to be refractory to radiotherapy. We have also found the drug to be effective in some individuals who had been resistant to hormonal therapy. Conversely, a few patients who had proven to be sensitive to hormonal agents and relapsed were resistant to 5-fluorouracil. A control series comparing the response of 5-fluorouracil and an alkylating agent was not run; however, it is our impression that a higher percentage of patients with carcinoma of the breast responds favorably to 5-fluorouracil than to any of the alkylating agents now in use. The present policy of the Cancer Chemotherapy Group at Jefferson is not to use standard chemotherapeutic agents until resistance to hormonal agents has been demonstrated. If extensive hepatic disease is present or if the patient is critically ill, 5-fluorouracil may be preferred initially since in our experience the use of hormonal agents in such patients has been disappointing. With 5-fluorouracil, several significant but relatively short term responses were seen in patients with severe, symptomatic metastatic liver disease. When a favorable response occurred to 5-fluorouracil, improvement was commonly seen within 14 days; with hormonal agents, four to six weeks were usually required before improvement was noted. Unlike the results seen with hormonal agents, the percentage of individuals with soft tissue disease, bony disease, and visceral disease who responded was approximately the same. Again, as a rule, the duration of remission was relatively short, but there were more remissions

lasting over three months in patients with carcinoma of the breast than there were in patients with carcinoma of the gastrointestinal tract. We had nine patients with carcinoma of the breast whose disease had proven to be hormonally unresponsive who were kept quite comfortable and active with repeated courses of 5-fluorouracil for periods of nine months to two years. At the present time, despite the greater hazard with the use of this drug, we feel that 5-fluorouracil is preferable to alkylating agents in those patients with metastatic carcinomas of the breast who require non-hormonal chemotherapy.

CARCINOMA OF THE LUNG

Nine patients with squamous or anaplastic carcinomas of the lung were treated. Only one showed any evidence of response, and this was quite short-lived. Four patients with adenocarcinoma of the lung were treated. Significant response was seen in only one patient. At the present time, we do not believe that 5-fluorouracil is of significant value in the therapy of carcinoma of the lung. Other individuals are investigating the use of combinations of 5-fluorouracil with other modalities of therapy such as radiotherapy (29), and it is possible that in the future the drug may be of some value when used in this manner.

MISCELLANEOUS CARCINOMAS

Although a large variety of lesions was treated, the numbers were too small to obtain evidence as to the percentage of each group that may be expected to respond. Several of the patients had interesting responses. For example, one patient with osteosarcoma had three objective remissions from 5-fluorouracil and was kept quite comfortable for close to a year with the drug. This woman's tumor was unusual also in that it showed a remarkable degree of radiosensitivity for an osteosarcoma. Other observers have claimed good results in the therapy of carcinoma of the urinary

bladder, but we were unable to verify this claim (30). It is true that, unlike the series of patients with responsive bladder tumors reported, all of our patients had previously received radiotherapy which may have partially contributed to our poor results. A significant percentage of patients with carcinomas of the cervix and ovary has been reported to respond to 5-fluorouracil (31). Ovarian carcinoma commonly is sensitive to alkylating agents, and because of their lessened toxicity they are probably preferable for initial chemotherapy.

Several groups have correlated percentage response with extent of disease and condition of the patient (32). While in general, drug toxicity was greater in patients who had extensive hepatic disease or were cachectic, a significant number of patients in this series with far advanced disease had substantial but usually short remissions. It was rare to get repeated remissions in such individuals, and prolongation of useful life usually was short, of the order of one to four months. No apparent correlation existed in this series between site of metastasis or clinical condition of the patient and incidence of initial remission.

DISCUSSION

The value of an agent such as 5-fluorouracil is difficult to assess for several reasons. Regressions of carcinomas of the breast, colon, and stomach occur in a significant percentage of patients treated; however, these are always incomplete and usually of short duration. Toxicity is invariably seen when a therapeutic dose of the drug is administered according to the conventional regimen, and the toxicity is quite disturbing to the patient. The drug is potentially lethal. Our drug mortality figure is 6% which is close to that reported by several large groups (31). The chances are good that the mortality rate will be higher if the drug is used by individuals who are inexperienced in its use.

Despite these disadvantages we believe

that the drug appears to be of value in the treatment of selected patients with malignant disease. Symptoms commonly relieved by therapy include pain, intestinal obstruction, dyspnea, and dysphagia. A majority of patients treated requested treatment again when symptoms recurred despite the knowledge of the toxicity involved. While long-term control (a year or more) was unusual, it was seen in several of the patients treated in this series with repeated courses. Also, the patient felt he had not been given up, and that specific therapy for his illness was being attempted. Even when therapy did not cause tumor regression, in many cases it seemed to be of real value. However, because of the dangers and discomfort associated with the use of the drug, it appears important to confine its use to patients who are incapacitated by their disease and for whom better methods of management are not available.

These diseases present one of the most pressing problems in medicine today, and new methods of therapy are urgently needed. It is possible that a major breakthrough may occur in this field. None, however, is visible at the present time, and progress may well be slow and dependent upon the knowledge gained from present experiences with therapy. Various treatment modifications, such as the use of slow infusions of 5-fluorouracil, the use of derivatives of 5-fluorouracil such as 5-fluorodeoxyuridine, and combination of 5-fluorouracil with other drugs or radiotherapy are now being studied with the hope of providing a more efficient and less toxic mode of treatment. A good illustration of such a philosophy is the experience with the use of antifolic acid agents which, when first introduced, appeared to be drugs of only moderate value in one disease, acute leukemia of childhood. It now appears possible that the drug is capable of curing one type of malignancy, choriocarcinoma of the female (33), and is also of value in several other malignancies especially when used by

regional infusion (34). Advances of this type depend upon extensive and controlled clinical experiences and represent long-term as well as immediate therapeutic gains.

SUMMARY

The antineoplastic action of 5-fluorouracil is described. Antitumor effect is found in a wide variety of tumors, primarily adenocarcinomas of the gastrointestinal tract and breast. Remissions are short, but occasionally, repeated remissions can be obtained. Toxicity may be severe and the drug is a dangerous one to use. It is believed by this group that the drug has a definite though limited value in the therapy of certain malignancies of man.

ADDENDUM

Two case reports are appended to illustrate the type of response obtained with 5-fluorouracil.

CASE REPORTS

CASE 1

A 41-year-old woman had a radical mastectomy for carcinoma of the breast in September

1954. When first seen in September 1960, she was critically ill. Extensive pulmonary metastases with pleural effusion were present. She had ascites and a large infiltrating mass in the remaining breast. A cell block from the pleural fluid was positive for malignant cells. Because of her critical status, it was not believed that castration was feasible nor was it believed that there was time for testosterone to be effective. She was therefore treated with 5-fluorouracil and received six grams over a 16-day period. She had mild stomatitis, her white blood count fell to $2,400/\text{mm}^3$, and her platelet count fell to $70,000/\text{mm}^3$. The peripheral blood count was normal three weeks after therapy was completed. A dramatic regression of the pulmonary mass occurred as illustrated in Figure 3 A and B. The mass in the other breast shrank to one-third its original size. She remained well for 24 weeks, after which there was a slight recurrence of her pleural effusion. At this time, it was decided that surgical castration was the therapy of choice. This was performed with relief of her symptoms and disappearance of fluid. She remained well for another ten months when she developed a hemiparesis which progressed to a hemiplegia. No other evidence of disease could be found. Because of the localized nature of the disease, a course of cobalt beam therapy to the skull was started. Despite this, progression of symptoms occurred. She was started on 5-fluoro-

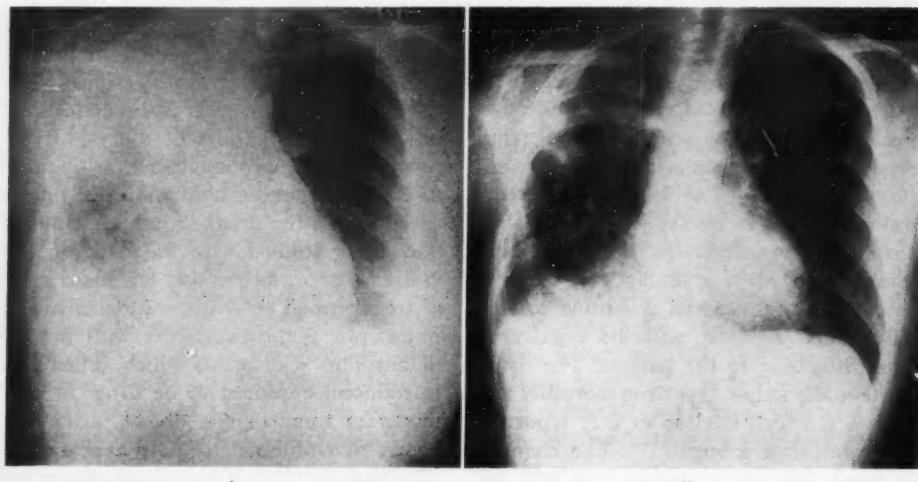


FIGURE 3. Case 1. A. X ray after paracentesis showing extensive pulmonary metastases. B. X ray showing regression of the pulmonary mass after treatment for 16 days with 5-fluorouracil six grams.

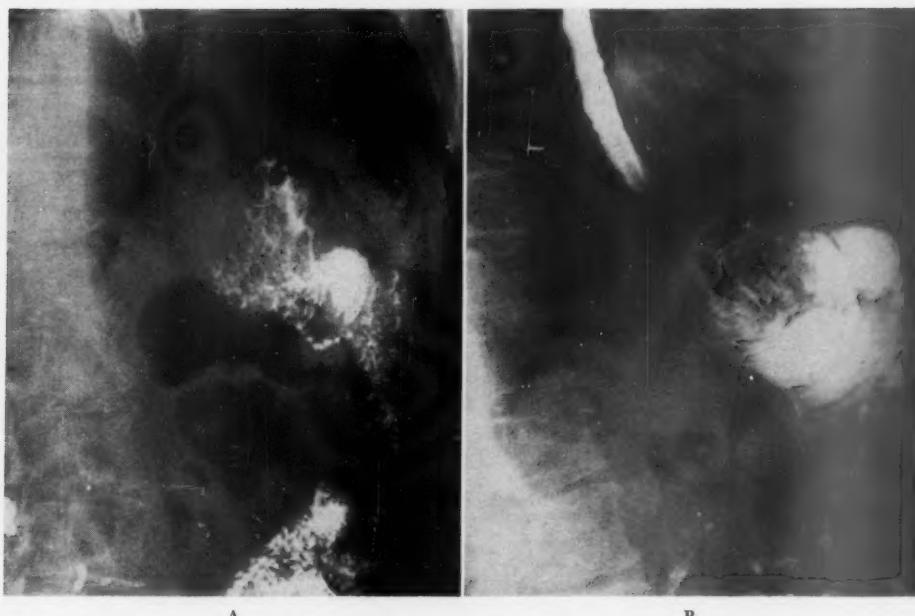


FIGURE 4. Case 2. A. Gastrointestinal series showing recurrence of carcinoma in the fundus of the stomach with almost complete obstruction of the lower esophagus. B. Gastrointestinal series after treatment for 12 days with 5-fluorouracil 4.5 grams.

uracil and received two grams. However, she developed status epilepticus and died during therapy. At autopsy a large cystic mass was found in the left parietal lobe, and small clumps of carcinoma cells were found in the wall of the lesion. She had a few nests of tumor cells in both pleural spaces and in the mesentery. However, these were minimal in extent.

CASE 2

A 66-year-old woman had a subtotal gastrectomy for carcinoma of the stomach in January 1959. At the time of surgery extensive nodal and hepatic metastases were present. She was well until August 1960 when she gradually developed dysphagia. A gastrointestinal series at that time showed a recurrence in the fundus of the stomach with almost complete obstruction of the lower esophagus. Before therapy, she was unable to swallow anything but small sips of water. In September 1960, she received 4.5 grams of 5-fluorouracil over a 12-day period with mild stomatitis and moderate leukopenia (minimal white blood count of $3,800/\text{mm}^3$, mini-

mal platelet count of $100,000/\text{mm}^3$). Her symptoms improved significantly and on discharge she was able to eat solid foods without difficulty. Figure 4 A and B demonstrates her gastrointestinal series before and after therapy. She was well for ten weeks when her symptoms returned, and she received another course of 5-fluorouracil with symptomatic improvement. The second remission lasted eight weeks. At this point it was decided to treat her with combined radiotherapy (cobalt beam) to the fundus of her stomach and 5-fluorouracil over a four-week period. She again had objective evidence of shrinkage of her gastric lesion and subjective improvement for 11 weeks. At that time she suddenly developed severe abdominal pain, ascites, and high fever with a rigid abdomen. She was treated conservatively with intestinal drainage and antibiotics. However, she gradually lapsed into coma and died. No autopsy was obtained.

ACKNOWLEDGMENT

The 5-fluorouracil was supplied by Hoffmann-La Roche Inc., Nutley, New Jersey.

SUMARIO IN INTERLINGUA

Es describite le action antineoplastica de 5-fluorouracil. Effecto anti tumor es notate in un extense varietate de tumores, primariamente adenocarcinomas del vias gastrointestinal e del mammae. Nos ha tractate 169 patientes con incurabile carcinomas. De istes, 37 habeva carcinoma del intestino crasse, e 27% experientiava un remission objective. Trenta-octo patientes con carcinomas mammari esseva tractate, e 29% de istes habeva objective responsas al droga. Remissiones habeva usualmente un duration de minus que tres menses, sed retractamento esseva possibile in certe casos.

A vices le toxicitate drogal esseva sever. Le droga habeva in nostre experientia un mortalitate de 6%. Nos opina que le droga ha un definite, ben que restringite valor in le therapia de certe malignitates human.

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Paradoxical Response of Metastatic Breast Cancer to 17-Ethyl-19-Nortestosterone

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WHEREAS THE BENEFICIAL EFFECT OF TESTOSTERONE in the palliative treatment of breast cancer has been well established (1), it has not been as generally appreciated that this hormone may exert an adverse effect on the course of this disease in some patients. Farrow and Woodward (2) were the first to point out that in occasional patients testosterone produces a dangerous rise in serum calcium. Since then, a number of reports (3-5) have appeared of severe toxic reactions, characterized by hypercalcemia, uremia, and coma occurring in patients with extensive osteolytic metastases from breast cancer during treatment with both androgens and estrogens. Pathological studies in fatal cases revealed extensive calcium deposition in renal tubular epithelium, lungs, gastric mucosa, and pancreas.

Because of the undesirable masculinizing side effects of testosterone, a variety of its derivatives having a higher ratio of anabolic to androgenic activity have been employed with varying degrees of success in the treatment of mammary cancer (6-9). Like testosterone, some of these compounds have been observed to stimulate as well as to suppress cancer growth. When administer-

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ing these agents, therefore, it is of the greatest importance for the physician to recognize promptly those patients in whom androgens have an adverse effect, so that their administration may be discontinued or modified before irreparable damage is done.

The purpose of this report is to present the adverse as well as the favorable effects of treatment with 17-ethyl-19-nortestosterone (norethandrolone *) in ten patients with extensive osseous metastases from breast cancer. In this series, two patients responded adversely, three favorably, and five not at all, results which parallel closely those observed with testosterone in a much larger series (10). The signs and symptoms of an exacerbation of tumor growth are the same whether produced by testosterone, its synthetic analogues, or estrogen. Evidence will be presented that this untoward effect of norethandrolone may be due to its conversion *in vivo* to estrogens.

METHODS

The rate of tumor growth was judged subjectively by symptoms of bone pain, general malaise, nausea and vomiting, and objectively by fever, inflammatory changes in visible metastases, and the quantity of calcium excreted in the urine on a dietary intake of less than 200 mg of this ion daily. Serum calcium, phosphorus, and alkaline phosphatase were measured by standard methods. Urine calcium was determined by a multichannel flame photometer after precipitation of phosphorus with stannous chloride (11). Urinary estrogens were estimated as total fluorescent phenolic steroids according

* Supplied by the Searle Company.

to the method of Engel, Slaunwhite, Carter, and Nathanson (12). When sufficient amounts were available, the major urinary metabolites of estrogens were identified by countercurrent distribution.

CASE REPORTS

Case 1: A. D. (Figures 1 and 2), female, age 48, underwent a radical left mastectomy for carcinoma with axillary metastases at age 46, and bilateral oophorectomy one year later because of recurrences in the skin of the anterior chest wall. These continued to grow and back pain developed due to diffuse osteolytic metastases to the spine. Hypophysectomy resulted in marked diminution in the size of the skin metastases, but no relief of back pain. Marked hypercalciuria was noted. Following hypophysectomy, the protein-bound iodine was 1.6 $\mu\text{g}/100 \text{ ml}$, and no follicle stimulating hormone could be found in the urine. A trial of nor-

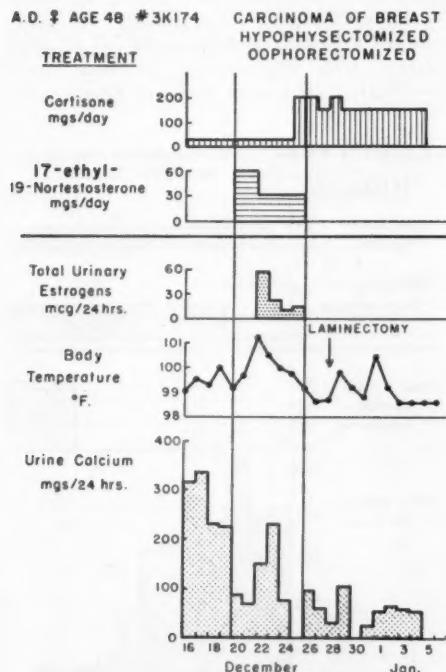


FIGURE 1. Adverse effect of 17-ethyl-19-nortestosterone on metastatic mammary cancer. Note rise in temperature on second day, increase in urinary calcium excretion on third day after initial fall, and high level of urinary estrogens with decrease to normal levels following reduction in androgen dosage.

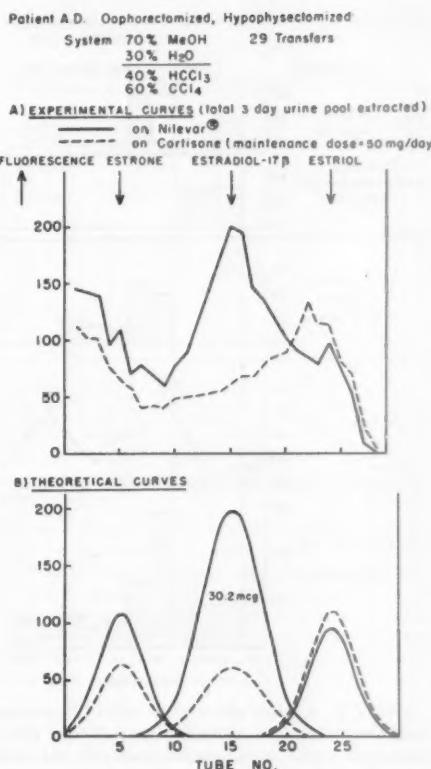


FIGURE 2. Countercurrent distribution of estrogens in the urine of patient A. D. (Figure 1) before and during treatment with 17-ethyl-19-nortestosterone. The rise in estradiol excretion during the treatment period is significant, that in estrone and estriol is not.

ethandrolone was then carried out. There occurred a transient fall in urine calcium excretion followed by a sharp rise. This was associated with fever, increase in back pain, and erythema, swelling and tenderness of the skin metastases. A high output of fluorescent phenols was present during norethandrolone administration, which fell to normal postmenopausal levels when the dose was reduced. Upon withdrawal of norethandrolone and administration of large amounts of cortisone the fever and pain subsided, but an emergency laminectomy had to be carried out because of spinal cord compression. This patient died two months later with cerebral metastases.

Countercurrent separation of urinary fluorescent phenolic steroids excreted during the period of norethandrolone administration re-

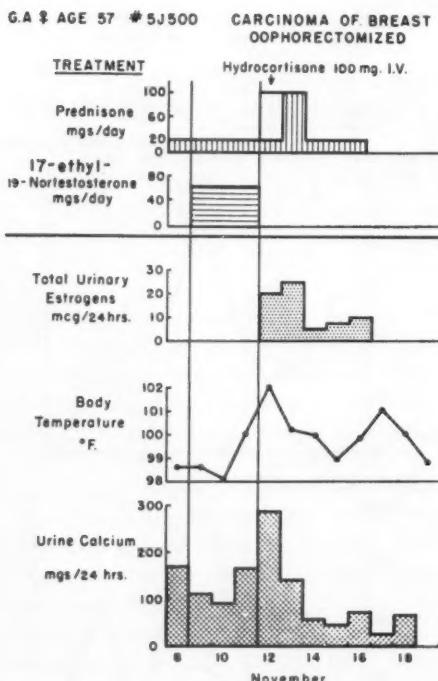


FIGURE 3. Adverse effect of 17-ethyl-19-nortestosterone on metastatic mammary cancer. Note rise in temperature and urine calcium excretion associated with relatively high levels of total urinary estrogens which fall to postmenopausal levels following cessation of androgen therapy and administration of large doses of adrenal cortical steroids.

vealed a significant increase in the estradiol fraction over the control period, equivalent to 10 µg per day (Figure 2). Diet and medication were the same in each period.

Case 2: G. A. (Figure 3), female, age 57, underwent a right radical mastectomy for carcinoma at the age of 43, and X-ray castration three years later because of local skin recurrences. She remained well until the age of 55, when osseous metastases appeared and were unaffected by bilateral oophorectomy. Prednisone provided symptomatic relief for 18 months. Bone pain then recurred, accompanied by hypercalciuria, and norethandrolone was administered as shown graphically in Figure 3. A transient fall in urine calcium occurred on the first two days, followed by a sharp rise. This was accompanied by fever, nausea, anorexia, and increase in bone pain necessitating immediate withdrawal of norethandrolone and administration of intravenous

hydrocortisone in large doses. An elevation of total urinary fluorescent phenols was observed immediately following norethandrolone administration with rapid fall to low postmenopausal levels two days after withdrawal of this medication. This patient died four months later with extensive liver metastases.

Case 3: H. C. (Figure 4), female, age 58, underwent a left radical mastectomy for carcinoma with axillary metastases at the age of 51. She had previously had a panhysterectomy at the age of 43. Two years later a solitary metastasis in the right humerus was controlled by X-ray therapy. Six years later widespread osteolytic metastases had developed with hypercalcemia and hypercalciuria, the liver had become enlarged, and the alkaline phosphatase had risen to 100 Bodansky units. The patient complained of fever, malaise, anorexia, and multiple bone pains. Treatment with triamcinolone resulted in no immediate improvement; norethandrolone was, therefore, started in doses of 30 mg daily (Figure 4). There followed a striking and sustained fall in urine calcium with improvement in bone pain. Shortly after the studies shown in Figure 4, the

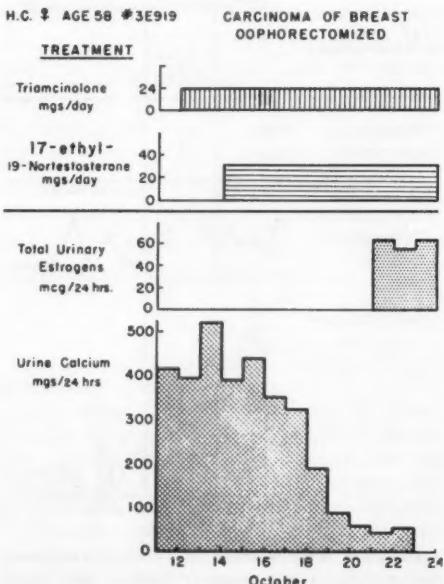


FIGURE 4. Favorable effect of 17-ethyl-19-nortestosterone on metastatic mammary cancer. Note striking fall in urinary calcium despite a high level of estrogen excretion during androgen administration.

patient became jaundiced, and she died with extensive liver metastases two months later.

Case 4: V. D. (Figure 5), female, age 58, had a right radical mastectomy for carcinoma with axillary metastases at age 45. Two years later axillary and supraclavicular recurrences and widespread osteolytic metastases were found. Oophorectomy, followed in one week by hypophysectomy, resulted in marked subjective and objective improvement. Following hypophysectomy the serum protein-bound iodine was $1.6 \mu\text{g}/100 \text{ ml}$, and follicle stimulating hormone disappeared from the urine. After six months, symptoms of calcium intoxication appeared with drowsiness, nausea, vomiting, hypercalcemia, and hypercalciuria. The hypercalcemia was relieved by the administration of large quantities of fluids and cortisone 300 mg daily, but hypercalciuria persisted until norethandrolone administration was begun six days later. Thereafter, the urine calcium excretion promptly fell to normal, and the patient showed striking subjective improvement. She remained free of bone pain while on norethandrolone therapy until her death six months later from liver metastases.

Case 5: E. P. (Figure 6), female, age 67, underwent a radical left mastectomy for carcinoma

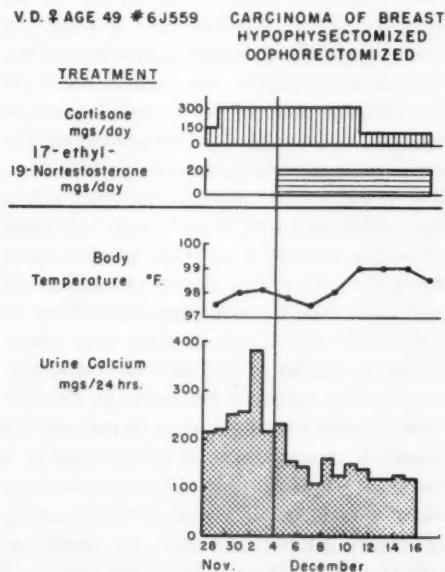


FIGURE 5. Favorable effect of 17-ethyl-19-nortestosterone on metastatic mammary cancer after large doses of adrenal cortical steroids failed to reduce urinary calcium excretion or bring about subjective relief.

E.P. ♀ 67 CA OF BREAST, POST-MENOPAUSAL

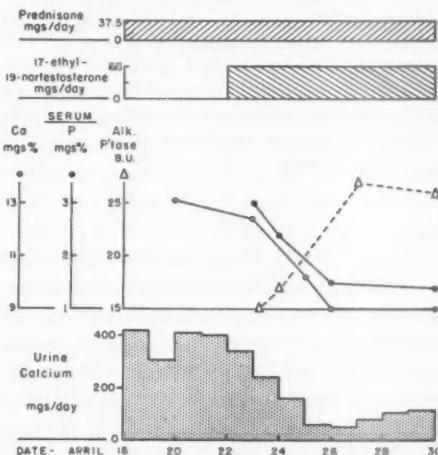


FIGURE 6. Favorable effect of 17-ethyl-19-nortestosterone on metastatic mammary cancer. Note striking drop in serum calcium and phosphorus levels and urine calcium excretion with reciprocal rise in serum alkaline phosphatase indicating new bone formation. Continued androgen administration was associated with disappearance of signs of calcium intoxication and relief of bone pain.

of the breast with axillary metastases in February, 1954, 23 years after a natural menopause. She remained well until October, 1958, when she developed a left brachial neuritis due to axillary and supraclavicular metastases. She improved on local X-ray therapy and adrenal suppressive doses of cortisone until September, 1959, when she experienced severe back pain, nausea, vomiting, and lethargy. Examination revealed widespread osteolytic metastases and signs of calcium intoxication, with a serum calcium level of $16.2 \text{ mg}/100 \text{ ml}$. On large doses of cortisone and forced fluids her symptoms improved, and the serum calcium was reduced to normal. Further gradual improvement followed the administration of androstane pyrazole,* 6 mg daily, with reduction of urine calcium excretion to low values and some objective X-ray evidence of recalcification at the sites of bone metastases during the next four months. The androstane pyrazole was then discontinued and within three weeks the signs and symptoms of calcium intoxication returned, with a serum calcium level of $13.6 \text{ mg}/100 \text{ ml}$. At this point she was given norethandrolone 60 mg daily by mouth. There ensued a very rapid and dramatic

* Supplied by the Winthrop Laboratories.

fall in serum calcium and phosphorus levels and urine calcium excretion, and a rise in serum alkaline phosphatase, indicating recalcification of bone, as shown in Figure 6. This was accompanied by marked subjective improvement which continued for another three months. Thereafter she developed increasing weakness, was unable to take oral medication, and died quietly at home.

DISCUSSION

Myers, West, Pearson, and Karnofsky (13) have clearly demonstrated that testosterone can induce a stimulation of the growth rate of breast cancer in a certain number of patients, which has been estimated as approximately 10% of all those treated. Based on the observations of many investigators (14-20) that testosterone and its analogues can be converted to estrogen in human tissues, Myers has postulated that the stimulating effect of testosterone on the growth of mammary cancer is actually caused by the estrogen to which it is converted in amounts more than sufficient to offset the beneficial effect of the androgen itself. As is the case with estrogen therapy, this untoward result of androgen administration is more apt to occur in the younger age group, before or soon after the menopause.

In the small series of cases presented above it would appear that norethandrolone like testosterone has had both an inhibiting and a stimulating effect on the growth of breast cancer. The finding of increased amounts of phenolic steroids during norethandrolone administration in the urine of the two patients whom it affected adversely supports the hypothesis of Myers et al. (13) that the adverse effect is due to excessive conversion of the androgen to estrogens by these individuals, whose tumors were presumably sensitive to estrogen stimulation. The isolation of measurable quantities of a substance having a partition coefficient by countercurrent distribution identical with that of estradiol in the urine of one of these castrated, hypophysectom-

ized females following norethandrolone administration (A. D., Figure 2) is particularly significant since this highly active estrogenic fraction can rarely be found in the urine of postmenopausal women. Further studies are in progress to measure the conversion of androgens to estrogens in patients with breast cancer by administration of testosterone labeled with carbon¹⁴ or tritium and measurement of the radioactive estrogens subsequently isolated from the urine.

It is of interest to note, on the other hand, the high urinary excretion of estrogens by patient H. C. (Figure 4) at a time when she was showing improvement on norethandrolone therapy. A rise in urinary estrogens has been noted previously in oophorectomized patients with extensive liver metastases similar to this one, and it has been thought to be due to the failure of the damaged liver to inactivate estrogens of adrenal origin (21, 22) or perhaps in this case, derived at least in part from the administered androgen. If this is true, the beneficial effect of norethandrolone on the osseous metastases in this patient may have occurred because of its conversion to an estrogen in an individual whose tumor was suppressed by this hormone, and perhaps this concept can be extended to explain the palliative effect of androgens on mammary cancer in general. It seems more likely to us, however, that the improvement on androgen therapy took place in spite of its conversion to estrogens since very much larger quantities of estrogens are ordinarily required to induce a remission in this disease, whereas very minute amounts can cause an exacerbation of the growth of a tumor susceptible to estrogen stimulation. Such a view implies that the suppressive action of androgens upon the mammary cancer cell is different from and unrelated to that of estrogens. Moreover, they do not act through the common pathway of pituitary inhibition, since two of the cases in this series whose tumors were affected by

norethandrolone, one favorably and the other adversely, had been previously hypophysectomized.

In the two cases exhibiting an over-all stimulation of tumor growth following norethandrolone administration, as evidenced by fever, pain, inflammatory changes in the skin lesions, and a rise in urine calcium excretion, these symptoms did not appear until the third day of treatment and were preceded by a transient fall in urine calcium. This observation suggests that a time interval was required for the conversion of norethandrolone to estrogens and that during this interval the androgen may have exerted a direct inhibiting effect on tumor growth, which was soon reversed by the increasing quantity of estrogens being produced.

The findings shown above should not be interpreted as contraindicating the use of androgens in the palliative treatment of breast cancer, which experience has shown to be helpful far more often than deleterious. Indeed, Kennedy et al. (5), and more recently Dederick and Hall (23), have shown that in a few patients with metastatic breast cancer an initial exacerbation of symptoms induced by both androgens and estrogens may be followed by a favorable response if treatment is continued. If therapy with either of these hormones is to be continued in the face of signs of exacerbation of the disease at the onset of treatment, however, it should be carried on only with the greatest caution and with the full realization of the possibly fatal complications of calcium intoxication. The slowly absorbed or long acting forms of androgens or estrogens should never be used initially. Whenever possible the effect of these hormones on the urinary excretion of calcium should be followed. The physician must be ever on the alert for signs of calcium intoxication and prepared to combat it by means of the administration of large quantities of fluids and adrenal cortical steroids (24).

SUMMARY

Among ten patients with advanced metastatic carcinoma of the breast treated with norethandrolone three were improved, two were made worse, and five were unaffected.

Evidence for the conversion of this substance to estrogens *in vivo* has been demonstrated in these patients and is cited as a possible explanation for its adverse effect in those individuals whose tumor is stimulated by estrogens.

The importance of watching carefully for signs of an exacerbation of cancer growth when administering androgens is emphasized.

ACKNOWLEDGMENT

We are indebted to Doctors Francis Moore, Andrew Jessiman, and Donald Matson for making their patients available to us for this study. The technical assistance of Miss Emma Lee Poindexter is gratefully acknowledged.

SUMMARIO IN INTERLINGUA

Inter 10 pacientes con ossee metastases ab carcinoma mammari le quales esseva tractate con norethandrolona, tres esseva meliorate, cinque esseva non-affectate, e duo esseva pejorate.

Indicaciones de un conversion del mentionate substantia in estrogenos esseva demonstratae in iste pacientes e es citata como un explicacion possibile del adverse effectos de norethandrolona in le individuos con tumores que es stimulate per estrogenos. Un simile grado de conversion del droga in estrogenos esseva etiam constatae in le caso de un paciente que se meliorava post le administration de norethandrolona. Es opinare que iste melioration resultava como efecto directe del androgeno plus tosto que ab su conversion in estrogeno, proque micrissime quantitates de estrogeno es producite per tal conversion, durante que vastemente plus grande quantitates es requirite pro effectuar un suppression del crescentia tumoris in le pacientes in qui iste responsa es evocate. Norethandrolona non age per inhibition pituitari, proque effectos favorable e etiam effectos adverse esseva notate post su administration in hypophysectomisate pacientes.

Quando androgenos es administrate a pacientes con carcinoma mammari, il es del plus grande importantia que on presta cautissime attention al possibile signos de un exacerbation

dcl morbo de maniera que iste forma de terapia pote esser suspendite ante que illo causa danos que non es reparabile.

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Myocardial Infarction—A Ten-year Experience in a Midwestern General Hospital

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THIS STUDY presents a ten-year experience in the diagnosis and management of acute myocardial infarction in a 150-bed general hospital in La Crosse, Wisconsin, a city of 45,000 inhabitants. The cases were seen in the Lutheran Hospital and the Gundersen Clinic, which are attached and which share common medical records and medical staff. Because the policy of this closed medical staff is to treat all heart attacks in the hospital, no patients were treated at home. It is believed, therefore, that this report approximates general medical experience with acute myocardial infarction in smaller midwestern hospitals of the United States.

MATERIALS AND METHODS

Clinic records of all patients diagnosed as having acute myocardial infarction from January 1, 1949, through December 31, 1958, were analyzed. These private patients came from all walks of life, from the city and within a radius of 100 miles; they were in the hospital from two to six weeks, the average being four weeks.

During this period, there were 351 white patients who had 435 acute myocardial infarctions. The diagnosis was based predominantly on clinical evidence and weekly (in some cases, daily) electrocardiographic changes (Leads I, II, III, aVR, aVL, aVF, and VI through V6). Emergency room facilities during the second half of the study provided an electrocardiograph so that all suspected cases received electrocardiograms immediately. Autopsy findings, when available, were utilized.

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Those patients whose records contained inadequate follow-up information either returned for re-evaluation or were sent questionnaires.

Incidence: Over the ten-year period an average of 43.5 acute myocardial infarctions was seen yearly, and the ratio of myocardial infarctions to general hospital admissions was 6.8 : 1,000.

The number of infarcts for each 1,000 general admissions per year is portrayed in Figure 1. The incidence rose in an irregular fashion from 2.5 in 1948 to 8.6 and 5.7 in 1957 and 1958, respectively.

Age and Sex: The youngest patient was a male, 24 years of age, the oldest, a female, 92 years of age. Of the 351 patients, the mean age for men was 58 years and for women, 65 years.

The highest number of cases for both sexes occurred in the group 65 to 69 years of age (Figure 2). The increase in the number of cases seen in men was most noticeable at age 40 to 44; in women the increase commenced ten to 15 years later in life. After age 69, the frequency of cases diminished in both sexes.

Two hundred and fifty patients (71.3%) were males and 101 patients (28.7%) were females.

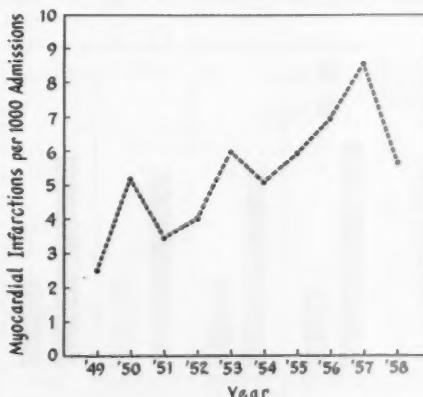


FIGURE 1. Number of myocardial infarctions per 1,000 general admissions per year.

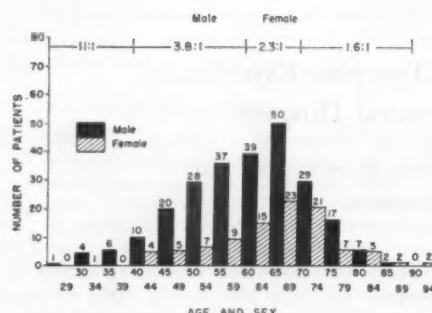


FIGURE 2. Age, sex, and sex ratio of 351 patients with myocardial infarction.

The over-all ratio of male to female was 2.5 : 1, but varied with age groups. Prior to age 40, a ratio of 11 males to one female was found (Figure 2); thereafter, the ratio decreased to 3.8 : 1 at age 40 to 60, 2.3 : 1 at age 60 to 70, 1.6 : 1 at age 70 to 85. At age 85 to 95, it reversed to more women than men.

Seasonal Influence: Figure 3 depicts the number of myocardial infarctions seen in each season of the year. While in men there were somewhat fewer cases in spring and summer, just the reverse was found in women so that seasonal influence over the total number of cases was not impressive.

RESULTS OF STUDY

ELECTROCARDIOGRAPHIC FINDINGS

Of 435 acute myocardial infarctions, 382, or 88%, had single or serial diagnostic electrocardiograms (Table 1). In 49 cases

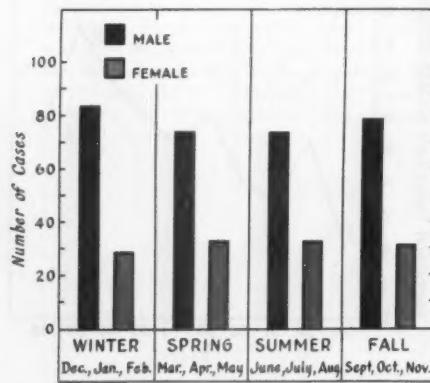


FIGURE 3. Myocardial infarctions related to seasons.

(11.3%) the electrocardiogram was not diagnostic; no case showed a normal electrocardiogram. Because of extenuating circumstances four cases did not have electrocardiographic examination. In the group with nondiagnostic tracings, left bundle branch block occurred in five (diagnostic electrocardiographic changes occurred in three additional cases of left bundle branch block and in 18 cases of right bundle branch block), and miscellaneous changes occurred in 44 instances. Clinically, the characteristics of the pain and associated symptoms strongly suggested cardiac origin; hospitali-

TABLE 1. Electrocardiographic Changes in 435 Acute Myocardial Infarctions

	Number	Per Cent
1. Diagnostic	382	88
2. Not diagnostic (non-specific)	49	11.3
(a) Left bundle branch block	5	1.1
(b) Miscellaneous (left ventricular hypertrophy, left ventricular strain, ischemia tachycardia, digitalis effect)	44	10.1
3. Not done	4	0.9

zation for several days did not detect symptoms and findings of other causes for the acute illness. Often serial sedimentation rates, leukocyte counts, and other tests, such as serum amylase, were consistent with myocardial infarction. Thus, in 11.3% of cases the electrocardiogram, although not normal, was not diagnostic, and the clinician was forced to make his diagnosis on clinical judgment and other laboratory findings.

Localization of cardiac infarction, based on serial QRST changes, is depicted in Table 2. The anterior wall was most commonly involved (53.6%) and was followed in order of frequency by the posterior wall (31.6%), lateral wall (2.6%), and subendocardium (0.93%). This general distribution

was common to both sexes, although no lateral wall infarct was detected in females.

Arrhythmias and conduction defects, as recorded in the electrocardiogram, are presented in Tables 3 and 4. In 84 cases the changes were observed in individuals with multiple infarcts, and several had more than one type of arrhythmia or conduction defect.

Fourteen types of arrhythmias were seen, the most common being sinus tachycardia in 13%. Sinus bradycardia was noted in 4.7%. The five most common ectopic arrhythmias were ventricular premature con-

TABLE 2. Electrocardiographic Localization of Myocardial Infarction*

	Male	Female	Total	Per Cent
1. Anterior	156	75	231	53.6
A. Anterior	104	48	152	35.3
B. Anterolateral	22	10	32	7.4
C. Anteroseptal	21	9	30	7.0
D. Extensive anterior	9	8	17	3.9
2. Posterior	101	35	136	31.6
A. Posterior	73	21	94	21.8
B. Postero-lateral	28	14	42	9.8
3. Lateral	11	0	11	2.6
4. Subendocardial	2	2	4	0.93
5. Non-diagnostic			49	11.4

* Based on 431 cases with serial electrocardiograms.

tractions in 9.5%, auricular fibrillation in 4.7%, auricular premature contractions in 3.2%, supraventricular tachycardia in 2.3%, and nodal premature contractions in 1.9%; together with other ectopic arrhythmias they represent an occurrence of 33.2%, or 132 of 431 infarctions. The total number of arrhythmias recorded was 208, or 48%.

Six types of conduction defects seen are listed in Table 4. In order of frequency they were: first-degree heart block, 6.2%; right bundle branch block, 4.1%; complete heart block, 2.3%; left bundle branch block, 1.8%; and second-degree heart block and Wenckebach's phenomenon. The total

TABLE 3. Cardiac Arrhythmias in Acute Myocardial Infarctions*

	No.	Per Cent
1. Sinus tachycardia	56	13.0
2. Ventricular premature contractions	41	9.5
3. Sinus bradycardia	20	4.7
4. Auricular fibrillation	20	4.7
5. Sinus arrhythmia	18	4.2
6. Auricular premature contractions	13	3.2
7. Supraventricular tachycardia	10	2.3
8. Nodal premature contractions	8	1.9
9. Wandering pacemaker	6	1.4
10. Nodal rhythm	4	0.9
11. Ventricular tachycardia	4	0.9
12. Ventricular fibrillation	4	0.9
13. Auricular tachycardia	2	0.5
14. Auricular flutter	2	0.5
Total	208	48.3

* Based on 431 cases with serial electrocardiograms.

number of conduction defects was 70, or 16.2%.

COMPLICATIONS

Analysis of complications of acute myocardial infarction was based largely on clinical evidence (Table 5). Shock attending the acute stage of infarction was the most common complication and was observed in 50 patients, of whom 30, or 60%, died during the acute phase. Second in frequency was left ventricular failure with pulmonary edema; 15, or 32.6%, died in the acute phase.

Pericardial friction rub was heard in 32 patients. In 22 of these the rub was audible

TABLE 4. Conduction Defects in Acute Myocardial Infarctions*

	No.	Per Cent
1. First-degree heart block	27	6.3
2. Right bundle branch block	18	4.2
3. Complete heart block	9	2.1
4. Left bundle branch block	8	1.9
5. Second-degree heart block	4	0.9
6. Wenckebach's phenomenon	4	0.9
Total	70	16.2

* Based on 431 cases with serial electrocardiograms.

TABLE 5. Complications of Myocardial Infarction
(351 Patients with 435 Infarcts)

	No. of Pts.	Per Cent of Pts.	Per Cent of Infarcts
1. Shock	50	14.2	11.5
2. Left ventricular failure	46	13.1	10.6
3. Pericardial friction rub	32	9	7.4
4. Gallop rhythm	14	4	3.2
5. Thromboembolic	14	4	3.2
6. Shoulder-hand syndrome	12	3.4	2.8
7. Cardiac aneurysm	9	2.6	2.1
8. Rupture of myocardium	4	1.1	

during the first three days of infarction, in five patients at the end of the first week, and in five other cases during the second week.

Fourteen patients had gallop rhythm. In seven of these it was noted on admission to the hospital and, in the other seven, later in the first week. Eight, or 58%, had left ventricular failure and four of these died within two weeks.

Thromboembolic phenomena were suspected in 3.2% of 435 infarctions. Pulmonary infarct or embolus was most common with thrombophlebitis in the lower extremities and cerebral embolus next in frequency (Table 6). Prothrombin time in most in-

TABLE 6. Thromboembolic Complications

Type	Days after Infarction	Pro-thrombin Time
1. Pulmonary infarct	6	—
2. Pulmonary infarct	11	51%
3. Pulmonary infarct	15	33%
4. Pulmonary infarct	24	39%
5. Pulmonary infarct	±30	±39%
6. Pulmonary infarct	3	43%
7. Pulmonary infarct	14	46%
8. Pulmonary infarct	57	54%
9. Thrombophlebitis, left leg	3	59%
10. Thrombophlebitis, right leg	14	50%
11. Thrombophlebitis, both legs	7	25%
12. Cerebral embolus	9	—
13. Cerebral embolus	8	—
14. Cerebral embolus	Undetermined	±47%
15. Embolus, right arm	22	±43%

stances was not within therapeutic range. These events occurred as early as three days and as late as 57 days after acute infarction; the highest incidence was between the eighth and the fourteenth days.

Shoulder-hand syndrome was recognized in 12 patients, one of whom experienced it one month after acute myocardial infarction. The onset in seven others occurred during the second and third month, in three patients between the fifth and seventh month, and in another case 15 months later.

TABLE 7. Recurrent Myocardial Infarction

	No. of Pts.	Per Cent	Interval between Infarcts
First attack }	351	100	—
Second attack }	60	17.1	Range (<1 mo to 96 mos) Average (32 mos)
Third attack }	15	4.3	Range (1 mo to 60 mos) Average (2½ mos)
Fourth attack }	7	2.0	Range (1 mo to 6 mos) Average (4 mos)
Fifth attack }	2	0.6	Range (7½ mos to 16½ mos) Average (12 mos)

Aneurysm of the left ventricle was strongly suspected or diagnosed in nine patients. Four of these had suggestive and four had diagnostic electrocardiographic changes; two of this group were later confirmed at autopsy and a ninth case diagnosed at necropsy. Two aneurysms were located posteriorly and seven, anteriorly, by electrocardiographic, roentgenologic, or autopsy findings.

Rupture of the myocardium was fatal and was found at autopsy in four cases, three of whom were hypertensive. Rupture took place on the seventh, eighth, twelfth, and twentieth days after acute infarction.

RECURRENT MYOCARDIAL INFARCTIONS

Eighty-four of 351 patients, 23.9%, developed multiple myocardial infarctions

treated in this hospital during the ten-year study (Table 7). Sixty, or 17.1%, had second attacks from one to 96 months (average 32 months) after the first infarction. Fifteen, 4.3%, had a third infarct one to 60 months (average two and one-half months) after the second infarction, and seven (2%) had a fourth infarct one to six months (average four months) after the third attack. Two patients were treated during a fifth episode seven and one-half to sixteen and one-half months (average 12 months) after a fourth infarction.

ANTICOAGULATION THERAPY

Anticoagulant therapy was begun gradually prior to 1949, and in 1952, became

TABLE 8. Hemorrhagic Complications

Complication	Number
Hematuria	30
Eccymosis	11
G. I. bleeding	9
Rectal bleeding	5
Nosebleed	5
Hemoptysis	4
Bleeding gums	2
Hematoma	2
Bleeding in middle ear	2
Menorrhagia	2
Total	72

routine, as almost all cases came under the care of physicians whose training in internal medicine emphasized this aspect of therapy. This is reflected by the small number, 71 (16%), of the 435 infarcts who received no anticoagulant drugs.

Attempts to evaluate the efficacy of these drugs in our experience were inconclusive, due to poor study controls. Of some interest, however, was the apparent low risk of drugs similar to coumarin. No deaths from hemorrhage occurred. Hemorrhagic complications encountered are listed in Table 8 and, for the most part, posed no serious problem.

TABLE 9. Status of 261 Patients One Year after Initial Myocardial Infarction

	No. of Patients	Per Cent
1. Dead	81	31
A. Died during initial infarct	55	21.2
B. Died after hospitalization	26	10
2. Alive	180	69
A. With coronary insufficiency	47	18
B. With myocardial insufficiency	12	5.0
C. With both	27	11
D. Asymptomatic	94	36

MORTALITY AND PROGNOSIS

Sixty-four patients died during treatment for an initial or recurrent infarction at this hospital; the over-all mortality rate was 18.2%. At the conclusion of the study, 149 of the 351 patients, or 42.4%, were known to be dead.

The condition of patients one year, four years, and ten years after initial myocardial infarction was investigated. In the one-year survival study (Table 9) there were 289 patients, of whom 28, or 9.7%, were lost to follow-up. In the remaining 261 patients, 81, or 31%, were dead; 55 of these, or 21.2%, died during hospitalization for initial infarction, and 26, or 10%, died after hospitalization. There were 180 patients, 69%, alive at the end of 12 months

TABLE 10. Status of 132 Patients Four Years after Initial Cardiac Infarction

	No. of Patients	Per Cent
1. Dead	64	48.5
A. Died during initial infarct	25	18.9
B. Died during subsequent infarct or from other causes	39	29.5
2. Alive	68	51.5
A. With coronary insufficiency	28	21.2
B. With myocardial insufficiency	4	3.2
C. With both	9	6.8
D. Asymptomatic	27	20.2

TABLE 11. Ultimate Cause of Death in 118 Patients with Acute Myocardial Infarction

Cause of Death	No. of Patients	Per Cent
1. Myocardial infarction	95	80.4
2. Cerebrovascular accident	7	5.9
3. Rupture of myocardium	4	3.4
4. Ventricular fibrillation	4	3.4
5. Congestive heart failure	2	1.7
6. Ventricular tachycardia	1	0.8
7. Uremia (nephrosclerosis)	1	0.8
8. Cachexia, dehydration	1	0.8
9. Mesenteric thrombosis	1	0.8
10. Cancer of pancreas	1	0.8
11. Cancer of the lung	1	0.8

and, of these, 59, or 23%, had symptoms of either coronary or myocardial insufficiency (angina pectoris was the criterion for coronary insufficiency, and either newly developed dyspnea or signs and symptoms of congestive failure was the criterion for myocardial insufficiency). Twenty-seven patients, 11%, had symptoms of both coronary and myocardial insufficiency. There were 94 patients, 36%, asymptomatic one year after initial myocardial infarction.

The status of 150 patients was determined four years after initial myocardial infarction. Eighteen patients had inadequate follow-up. Table 10 shows the cardiac situation in the remaining 132 patients. The dead numbered 64, or 48.5%; of these, 18.9% died during the initial attack, and 29.5% died subsequently of another myocardial infarct or from other causes. Survivors numbered 68 patients, 51.5%, and, in this group, 21.2% and 3.2% had symptoms of either coronary or myocardial insufficiency respectively. Symptoms of both occurred in 6.8% of patients. Twenty-seven patients, or 20.2%, were asymptomatic.

A small group of 14 patients had cardiac infarction in 1949; nine of these were dead within eight years and four were lost to follow-up. One male, age 66, was still alive ten years after his initial infarct; he had

been hypertensive prior to the first attack and had developed a second infarct four years after the first one; two years after the second attack he had symptoms of coronary insufficiency, but in the tenth year, he was asymptomatic.

CAUSES OF DEATH

In 31 cases of the 149 known to be dead at the conclusion of the study, adequate information regarding the cause of death was lacking. One hundred eighteen records were suitable for analysis.

Table 11 shows that myocardial infarction was the leading cause of death in over 80% of cases. Sixty-four of these patients died during the acute phase of their initial infarct. In the remaining 31 patients, 26.2%, death was sudden, i.e., relatives commented that the patient suddenly slumped over in his chair and died, walked across the living room and fell to the floor dead, or was found dead in bed.

Other fatal cardiovascular events were cerebral vascular accidents ("stroke") 5.9%, rupture of the myocardium 3.4%, ventricular fibrillation 3.4%, congestive heart failure 1.7%, ventricular tachycardia 0.8%, and miscellaneous causes of death, ranging from uremia to pulmonary carcinoma.

DISCUSSION

An experience of this type is influenced by the circumstances in which the physician sees the patient. All of these cases were seen in private practice by either general practitioners or men trained in internal medicine. The physician's fatigue, induced by a demanding schedule, very likely limited recording of finer observations detailed in reports from larger institutions.

Few reports in the literature cite the incidence of myocardial infarction in private general hospitals. It is possible that this varies as much as the 0 to 70% yearly mortality rate in four different types of hospitals in Houston, Texas (1). Gotshalk (2) found 6.3 cardiac infarcts per 1,000

discharged patients in Queen's Hospital, Honolulu, Hawaii. From a small hospital in New Jersey, Lipkin (3) noted nine acute myocardial infarctions per 1,000 admissions. Our own incidence of 6.8 per 1,000 admissions compares closely to that found in Honolulu, in spite of a practice and climate which more closely simulates that found in New Jersey.

While the number of cardiac infarctions seen each year rose significantly, the incidence of infarction per 1,000 general admissions per year more than tripled, suggesting that the rise in general admissions per year would not explain the increasing number of heart attacks treated. We are also reluctant to state that the community has experienced more coronary occlusive disease. It would seem more plausible that other factors peculiar to the institution were at work. Improved emergency room facilities attracted rather than repelled ambulance drivers. Higher diagnostic acumen, in part due to routine preoperative electrocardiograms in older patients, and a greater index of suspicion by physicians for unexplained chest pains, surely were influential. Lastly, the reputation of the physician group developed more towards non-surgical specialization, particularly of the heart. These and many other subtle factors were involved but none of them can be analyzed practically.

The high incidence of 1957 is unexplained. Subsequently, the rates for 1959 and 1960 were determined to see if the rising incidence continued; this proved to be true, with 8.6 and 7.2 infarctions per 1,000 general admissions seen respectively.

The age range in which myocardial infarction occurred and the age group with the highest incidence reported here is in general agreement with numerous surveys (4-11). The sex or hormonal influence on cardiac infarction has been emphasized by others (6, 7, 10-15); it is amplified by the diminishing sex ratio with age noted in this study.

Seasonal influence on myocardial infarction reported in the literature is variable. Most studies stress a higher incidence in fall, winter, and spring (16-20), while others have found the incidence to be highest in summer (21). Teng and Heyer (22) suggest that it is the sudden change in temperature which is important. Our neighbors in the south in Kentuckiana found the highest number of cases to occur in winter and spring (23); others report no such influence (10). Our experiences in a climate where weather conditions change abruptly and seasonal variations are pronounced indicate negligible influence.

The 11.3% incidence of non-diagnostic electrocardiographic changes reported here is at variance with other studies; for example, Weiss (16), found an incidence of 17% when these were correlated with autopsied cases. Holzman (24) found negative tracings in 2% of his cases. Other reports (25-27) agree that the electrocardiogram is never strictly normal in acute myocardial infarctions, and this was our experience. In contrast, Johnson, Achor, Burchell, and Edwards (28), in a clinicopathologic study of unrecognized myocardial infarction, found 38% of studied autopsies with electrocardiograms that did not support post-mortem diagnosis. That infarction of the heart can occur without changes in the electrocardiogram has been demonstrated experimentally (29-31).

We believe it is pertinent to add that cardiac infarction can occur in about 11 to 12% or more of cases without characteristic QRST changes, and the clinician must rely on clinical judgment and other laboratory findings. It may well be that new techniques involving tridimensional concepts of electrocardiography will uncover cardiac infarcts hitherto unrecognizable.

Most troublesome electrocardiographic alterations obscuring diagnostic changes in this study comprised a miscellaneous group of "borderline" ST segment and T wave changes, digitalis effect, and left ventricular

hypertrophy and strain. All cases of right bundle branch block here reported and almost all reported by Sommerville and Wood (32) showed diagnostic changes. As would be expected, left bundle branch block was less revealing, with 62% not showing diagnostic changes (Sommerville and Wood report about 52%).

The anterior wall is usually infarcted in slightly over 50% of cases (8, 10, 19, 28, 33). In this study, the incidence was 53%, but Pell and D'Alonzo (21) found the posterior wall to be more commonly involved. It is interesting to note how closely the site of infarct followed the same distribution for both males and females in this study. Absence of lateral wall infarction in females noted here is probably the result of a smaller number of cases in women.

The incidence of ectopic rhythms and conduction defects depends largely on the time and frequency of electrocardiograms taken during acute infarction. Cole et al. (8) found 24% ectopic rhythms and 17.7% conduction defects compared with 33.2% (exclusive of sinus tachycardia and bradycardia) and 16.2%, respectively, in this study.

Mortality rates for acute myocardial infarction vary from 15 to 60% (3, 4, 8, 10, 21, 34-36). Mortality of 25% during the first month of infarction appears to be representative (9). In this study, the over-all mortality was 18.2%; this included the period when patients were in the hospital during initial or recurrent infarction, as well as deaths within one hour of reaching the emergency room.

Survival studies again vary with criteria used. Smith and Carter (35) indicate that the mortality rate one year after infarction is 25%; it drops to 8% if based on those patients surviving the first two months (37). In this study, we found that 31% of patients, including those hospitalized, died within one year of initial infarction; of those surviving the first month, 10% died within the first year. Reported mortality rates four to six years after acute myocar-

dial infarction vary from 34 to 51% (8, 33, 35, 37, 38); most of these are based on survival of the first or second month. The mortality rate (48.5%) four years after initial infarction found here includes patients who died within 24 hours of infarction; the mortality rate of those surviving the first month was 36.4%.

In private practice clinical diagnosis of thromboembolic complications after myocardial infarction, unless seriously jeopardizing the patient's welfare, is at best an educated guess. The low incidence reported here, the widely varying incidence of pulmonary embolus (7 to 29%) reported in the literature (39-43), and the nearly doubled incidence found at autopsy (39, 42, 43) tend to support this supposition.

The incidence of other complications for similar reasons is difficult to assess. Shock, for example, generally considered to be a common manifestation, is "severe" and of major concern to the clinician in the minority of cases, perhaps 10 to 16% as reported by Selzer (44), White, Moore, and Marmarston (45), and 11.5% in this study. The ominous prognosis in those cases attended by cardiogenic shock, left ventricular failure, and gallop rhythm is reflected in the increased mortality observed in these patients and documented elsewhere (4, 8, 11, 26, 44).

Our experience with anticoagulant therapy is inconclusive. It does point up the fact that, in hospitals of this size, the efficacy of this treatment is not accurately assessed because of inadequate controls.

Significant or serious hemorrhagic complications of anticoagulant therapy are reported in 1 to 13.2% of cases (46-50). Bleeding manifestations from such drugs in this study were recognized in 25.7% of cases and ranged from the common (usually microscopic hematuria) to the unusual (middle ear hemorrhage). Seldom was it necessary to stop the drug permanently unless hemorrhage was severe and from a precarious location. Although our study

includes no deaths from anticoagulants, the incidence of deaths from this cause is reported to be 0.5 to 1.1% (46, 50).

Survival from an initial cardiac infarction means that in the large majority of cases death will ultimately be caused by another infarction (8, 33, 37); this was true in the majority of cases reported here where the average interval between infarcts was greatest between the first and second, and less between subsequent episodes. In addition, the clinical status of these patients was found to deteriorate with time; one year and four years after initial infarction, 37% and 20%, respectively, were asymptomatic.

SUMMARY

1. This analysis relates a ten-year experience in diagnosis, treatment, and prognosis of 351 patients with acute myocardial infarction who were seen in a general hospital serving a small midwestern city.

2. There were 6.8 myocardial infarctions for every 1,000 admissions. The incidence per 1,000 general admissions per year increased significantly during the decade.

3. Cardiac infarction occurred in patients as young as 24 years of age and as old as 92; the average age for men was 58, for women, 65. The over-all ratio of men to women was 2.5 : 1. This ratio decreased in older age groups until women eventually outnumbered men. No seasonal influence was noted.

4. The electrocardiogram was not diagnostic in 11.3% of cases, showed the anterior wall as the most common site of infarction, recorded numerous arrhythmias and conduction defects, and demonstrated characteristic changes for infarction in all cases with right bundle branch block and in 38% of cases with left bundle branch block. No patient with acute myocardial infarction had a normal electrocardiogram.

5. While the expected complications were observed, their true incidence was questionable, as they depended on the at-

tending physician's inclination to record accurate observations. Shock, which was of major concern to the attending physician, occurred in 11.3% of cases.

6. Twenty-four percent of 351 patients were treated for subsequent myocardial infarctions. There was a tendency for the interval between attacks to shorten.

7. The efficacy of anticoagulant therapy was not accurately assessed. No deaths or life-threatening hemorrhages attributable to it were observed.

8. The over-all mortality during the acute phase was 18.2%. At the end of the period, 42.4% of the patients were known to be dead. One year after initial myocardial infarction (not based on survival of the first or second month) 31% were dead and 36% of those alive were asymptomatic. Four years after initial myocardial infarction (not based on survival of the first or second month) 48.5% were dead and 20.5% of survivors were asymptomatic.

9. Of the 149 patients known to be dead at the end of the ten-year period, the ultimate cause of death in a large majority was myocardial infarction.

SUMMARIO IN INTERLINGUA

Iste analyse es concernite con un experientia de 10 annos in le diagnose, therapia, e prognose de 351 patientes con acute infarcimento myocardial, vidite in un hospital general que servi un minor citate del statounitese west central. Le incidentia del infarcimentos esseva 6,8 pro omne 1,000 hospitalisationes. Le incidentia del infarcimentos pro 1,000 hospitalisationes per anno montava significativemente in le curso del decennio.

Infarcimento cardiac occurreva in patientes de etates de inter 24 e 92 annos. Le etate media pro masculos esseva 58 annos, pro femininas 65. Le proportion general inter le sexos esseva 2,5 masculos pro 1 feminina. Tamen, iste proportion declinava in le grupplos de etates plus avantiante, e finalmente le numero de patientes feminin excedeva le numero del masculos. Nulle influentia saisonal esseva notate.

In 11,3% de nostre casos, le electrocardiogramma non esseva diagnostic. Tamen, nulle

paciente con acute infarto myocardial havia un electrocardiogramma normal.

Esseva observe le expectate complicaciones, sed le ver incidentia de illos esseva questionable, proque le notation o non-notation de illos in le dossiers dependeva del inclination del medico de registrar su observationes accuratemente. Choc occurreva in 11,3% del casos.

Le mortalitate general in le phase acute esseva 18,2%. Al fin del periodo, 42,4% del pacientes esseva cognoscitamente morte. Un anno post le occurrentia initial del infarto myocardial (non restringite al superviventes de un o de duo menses), 31% esseva morte. Le 69% qui viveva includeva 36% qui esseva asymptomatic. Quatro annos post le occurrentia initial del infarto myocardial (non restringite al superviventes de un o de duo menses), 48,5% esseva morte, e 20,5% esseva asymptomatic. Pro le majoritate del 149 pacientes qui esseva cognoscitamente morte al fin del periodo de dece annos, le ultime causa de morte esseva infarto myocardial.

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Anticoagulant Therapy in the Relatively Young Male with Myocardial Infarction

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A CUTE MYOCARDIAL INFARCTION represents a major cause of death in all medically advanced countries of the world. Its immediate mortality rate in this country ranges from 16 to 64%, with an average approaching 30% (1-4). During the past two decades anticoagulants have been added to the rather meager therapeutic program of rest, sedation, oxygen, and analgesics. The vast majority of reports concerning such therapy have been quite favorable, demonstrating a reduction in both mortality and morbidity (5-9). A notable exception has been the work of Russek and Zohman (10), whose good-risk patients treated without anticoagulants have a mortality rate of only 3.5%. It is evident from a review of the literature that the younger and healthier individuals survive much more frequently. Reference has been made to the young, mild coronary patient whose acute course is consistently uncomplicated, whose mortality is nil, but who still, statistically, suffers the long-range reduction in life expectancy of other infarction patients (11, 12). The main arguments against many current reports supporting the generalized use of anticoagulant therapy are that they consist of the older, more complicated general hospital type patients not representative of cases seen in private practice, and that for control groups they include early deaths

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and patients in whom anticoagulants were contraindicated, or had been discontinued. In setting up a valid experimental design these are considered a poor substitute for an alternate case control group. At DeWitt Army Hospital the majority of males with myocardial infarction are relatively young and otherwise healthy. They appear to have an extremely benign acute course and almost all recover. It was the belief of one of us that this young, mild coronary occlusion patient who experienced no resultant circulatory system impairment had no real need for anticoagulant therapy. Accordingly, anticoagulant therapy was not instituted on any new patients with myocardial infarctions who were admitted to this hospital over a period of 20 months. Except for the omission of anticoagulants, the treatment of patients admitted previous to this period and subsequent to it was identical.

The purpose of this paper is to present a series of these patients (half of whom received no anticoagulant therapy) to determine the benefit of anticoagulant versus no anticoagulant therapy, and to compare this group with other acute myocardial infarction series from the literature.

METHODS AND MATERIALS

Basic treatment of the acute cases at this hospital included two weeks of absolute bed rest with restricted diet, oxygen therapy, sedation, and narcotics as necessary for pain relief. The duration of the pain determined the period of oxygen therapy. Graduated ambulation in the third week led to convalescence at home during the fourth week. Near normal activity, except for strenuous exertion, was anticipated

by the end of the third month. Routine serial electrocardiograms, hemograms, sedimentation rates, and glutamic oxaloacetic transaminase levels were obtained. Chest X rays, serum lipids, cholesterol, blood sugars, and other routine laboratory data were available for most patients. Both heparin and coumarin derivatives (usually warfarin sodium) were used in most of the cases receiving anticoagulants, the heparin being discontinued once prothrombin times were in a therapeutic range. All patients were followed at least three months after infarction. Seventy of the 100 patients (including all 50 of those not taking anticoagulants) were personally treated and followed by one or both of the authors. The remaining 30 patients were checked by other physicians on the staff of this hospital.

Criteria for diagnosis included a typical clinical history in all cases, and serial electrocardio-

TABLE 1. Average Age, Range, and Distribution of the Treated, Control, and Total Groups

	Treated	Control	Total
Average	44.2	44.4	44.3
Age range			
29-34	1	2	3
35-40	16	11	27
41-45	13	21	34
46-50	14	10	24
51-56	6	6	12
Totals	50	50	100

graphic changes in all but one case, the patient who died. Leukocytosis, elevation of sedimentation rate, and elevated transaminase levels occurred in 90, 88, and 70%, respectively. As a final check, 83% of the patients, being on active duty, were required to meet a Medical and Physical Evaluation Board who reviewed the complete hospital course. In no instance was there disagreement with the diagnosis. By the criteria of Wright et al. (6), all 50 of the patients receiving anticoagulants were considered to be adequately controlled.

The records of all male patients admitted to DeWitt Army Hospital with the diagnosis of acute myocardial infarction between January 1956 and October 1960 were examined. Of 120 such cases, 17 were eliminated, six because of doubt concerning diagnosis, six because of inadequate records, and five because their age exceeded 60 years. Of the remaining 103 patients, three were excluded from the comparative study because their early deaths prevented

TABLE 2. Type and Location of Infarction

Type/ Location	Intramural	Transmural	Total
Anterior	27	19	46
Posterior	23	31	54
Total	50	50	100

institution of proper therapy. Two of these died within two hours of reaching the emergency room, and the third survived only 11 hours. Of the remaining 100 patients, 50 received anticoagulant therapy on admission, and 50 did not. The temporal distribution of these 100 patients treated with, without, and again with, anticoagulant therapy is as follows: January 1956 to September 1958, 34 consecutive anticoagulant treated cases; October 1958 to May 1960, 50 consecutive non-anticoagulant treated cases; and May to December 1960, 16 consecutive anticoagulant treated cases.

The average age of the 100 patients in this group was 44 years. Table 1 shows the age range and average ages of the treated and control groups. The age range was 29 to 56 years; 85% of the patients were between 35 and 50 years old.

Table 2 shows the type of infarction and location. Half of the infarctions were intramural, and slightly more than half were posterior. There was no difference between the treated and control groups as to size or location of the infarction. By intramural we refer to the usual electrocardiographic features of an acute infarction and its evolution without the formation of Q waves.

Eighty-nine of the 100 patients were hospitalized for their first myocardial infarction. Of these, 43 were in the group treated with anticoagulants, and 46 were from the control group (Table 3). Two patients incurred their infarction while on anticoagulants.

Past medical histories were quite benign, indicative of the patients' generally good health.

TABLE 3. Infarction Number

	Treated	Control	Total
One	43	46	89
Two	6	4	10
More	1	—	1
Total	50	50	100

Family histories were not unusual, although 50% were positive for arteriosclerotic heart disease.

RESULTS

Mortality: Of the entire group of 100 patients whose course was studied from admission to three months following infarction, only one patient died. He was not on anticoagulants, and he died of ventricular fibrillation 68 hours after admission. Except for the clinical suspicion, there was no evidence of infarction during life, and autopsy showed a tiny intramural infarction involving the interventricular septum. Even when we add the three patients not included in this series of 100 because they died one and one-half, two, and 11 hours after hospitalization, the fatality rate is only 3.8%. There was no thromboembolic death in the entire series.

Morbidity: Table 4 outlines the complications, other than thromboembolic, in the treated and control groups. This heterogeneous group of complications could be interpreted to favor either method of treatment, although they suggest that the treated group did contain several larger, more severe infarctions. A sizable percentage (49%) of the patients did display angina at the end of three months on return to normal activity. Complications of anticoagulant therapy were limited to a single non-fatal case of gross hematuria.

Thromboembolic Complications: Pulmonary emboli were more frequent in the

TABLE 4. Complications from Other Causes

Group Complications	Treated	Control	Total
Congestive failure	7	1	8%
Hypotension/shock	7	7	14%
Cardiac arrhythmia	5	2	7%
Pneumonia	—	1	1%
Bleeding	1	—	1%
Angina*	27	22	49%
Totals	47	33	80%

* On return to activity at the end of three months.

TABLE 5. Thromboembolic Complications

Group Complication	Treated	Control	Total
Extension of infarction	4	4	8%
Pulmonary embolus	4	1	5%
Cerebral embolus	—	1	1%
Peripheral embolus	—	—	0%
Venous thrombosis	1	2	3%
Totals	9 (18%)	8 (16%)	17%

anticoagulant group, and extension of the myocardial infarction occurred equally in the two groups. The single cerebral vascular accident, which appeared to be embolic, occurred in the control group. There were no peripheral arterial embolic phenomena. The total thromboembolic complication rate was 18% in the group receiving anticoagulants and only 16% in the untreated group, demonstrating no significant benefit from anticoagulant therapy in this series of patients (Table 5).

DISCUSSION

Several points deserve further comment. First of all, when speaking of the mortality or morbidity of myocardial infarction, one must define the patient group under discussion. The marked difference in mortality is well illustrated in the literature, where rates of 11 to 67% are found, depending on the ages and socioeconomic factors (1-4). Russek, for example, whose fatality rate in good-risk patients not treated with anticoagulants is only 3.5%, found a fatality of 60% in his poor-risk patients (10). These rates form the basis for his selective use of anticoagulants. While his statistics are clear and lead to obvious conclusions, few have been able to reproduce them. Many studies present just as strong an argument for anticoagulant therapy in all age groups. The best of these is a cooperative study by the Committee on Anticoagulants of the American Heart Association, edited by Wright et al. (5). However, even in this report it is noteworthy that while thromboembolic

complications were substantially decreased in patients below age 60, the fatality rate was not significantly changed by anticoagulant therapy. Both of these widely divergent studies agree on one point—that the young, otherwise healthy patient with a myocardial infarction has a much better chance of survival, and that this chance for survival is not substantially improved by anticoagulant therapy.

Myocardial infarction in soldiers aged 20 to 35 years has been quite thoroughly studied by several large autopsy series from the Armed Forces Institute of Pathology (13-15). It has been demonstrated that coronary atherosclerosis, a common finding in young American males, is almost invariably the cause of such infarction (16). Furthermore, with the lack of sufficient collateral blood supply, these infarctions are frequently fatal (17); the majority occur as sudden death (18), many are associated with preceding exertion in slightly obese individuals, and almost 50% show evidence of old subclinical infarction (19). These statements do not hold true if the individual has an infarction 15 years later, as illustrated by this series. On the other hand, the high mortality of older, complicated cases is well documented (20). Thus, as far as immediate survival is concerned, the optimal age for an infarction is between 35 and 55 years, when complicating diseases are still minimal and compensatory mechanisms for coronary flow are adequate.

The benignity of acute myocardial infarction in this series is all the more striking when one considers that our immediate mortality period was three months, whereas that of most series is only four to six weeks.

We believe a question remains as to the need for treating all acute infarctions with anticoagulant therapy. Perhaps larger series of selected patient groups such as this one will provide a more complete answer. From a practical viewpoint, often a decision must be made whether to transport an acute coronary case some distance from his home

or isolated assignment to a hospital where controlled anticoagulant treatment is available, or to leave the patient where he is and insure proper rest and basic therapy. In young males who were healthy previously, the results of this study indicate that if and when a choice must be made the latter is preferable.

SUMMARY

We have presented a series of 100 relatively young, otherwise healthy male patients treated for acute myocardial infarction at DeWitt Army Hospital. The average age was 44 years. Half of this series was treated without anticoagulants; otherwise treatment and type of infarction were quite similar. The 90-day mortality rate was 1% and occurred from nonthromboembolic causes in the control group. The uncorrected mortality, including deaths before adequate specific therapy could be employed, was only 3.8%. There was no significant difference between the thromboembolic complication rates of the two groups (18% in the group receiving anticoagulants and 16% in the control). The marked difference in age, mortality, and morbidity between this series of 100 young patients and other series composed of older general hospital patients is an important consideration. The authors believe that benefits derived from anticoagulant therapy for myocardial infarction correlate with the age of the patient and related medical debility. However, based on the present series, it is believed that anticoagulant therapy can be omitted in the young patient who is healthy otherwise, without causing any measurably increased morbidity or mortality.

SUMARIO IN INTERLINGUA

Es presentate un serie de 100 relativemente juvene masculos tractate pro acute infarcimento myocardial al Hospital Militar De Witt. Alteremente illes omnes esseva de sanitate normal. Lor etate medie esseva 44 annos. Un medietate del serie esseva tractate sin anticoagulantes, le altere

con anticoagulantes. A parte isto, le tractamento in le duo grupplos esseva multo simile. Etiam le typos de infarcimento representante in le duo grupplos esseva simile. Le mortalitate total in iste serie esseva 1% intra 90 dies. Le victimia esseva un paciente qui non recipeva anticoagulantes, sed le causa de su morte non esseva thrombo-embolismo. Nulle significative differencia del incidentia thrombo-embolic esseva notate inter le duo grupplos. Embolo pulmonar, cerebral, o peripheric, thrombose venose, o extension del infarcimento occurreva in 18% del pacientes qui recipeva anticoagulantes e in solamente 16% de illes tractate sin anticoagulante. Esseva opinare que le bassissime mortalitate esseva relationate al condition physic general del pacientes, a lor estates, e al dimensiones del infarcimentos. Le acute, adequate therapia anticoagulante que esseva usate in iste gruppo de pacientes habeva nulle efecto del toto super le morbiditate o mortalitate.

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Accelerated Thromboplastin Generation in Acute Arterial Occlusion Complicating Arteriosclerosis Obliterans

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WHAT PART, if any, thrombosis plays in the development of arteriosclerosis is still unsettled; however, there is agreement that thrombosis is the terminal event in the arterial occlusion of the extremity affected by arteriosclerosis obliterans. Pathologic study of the arteries of limbs amputated for advanced arteriosclerosis obliterans has shown that thrombosis is responsible for at least part of the arterial occlusion in all (1).

Within the group of persons with arteriosclerosis obliterans are patients whose course is a chronic one, their only symptom being intermittent claudication; the course of other patients, however, is complicated by sudden arterial occlusion often resulting in severe ischemia or gangrene of part or all of an extremity. In considering the latter group of patients, both clinical and pathologic evidence suggest that some change in coagulability of the blood may be responsible for the sudden thrombotic occlusion of an arteriosclerotic artery.

In the past, studies of blood coagulation in persons with arteriosclerosis obliterans have suggested that hypercoagulability of the blood occurs in some cases (2-4). Unfortunately, the tests then available lacked the refinements necessary for minimizing the inherent variables of *in vitro* testing or

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delineating the cause of any existent hypercoagulable state.

THE PATIENTS STUDIED

The coagulation mechanism of 105 patients with arteriosclerosis obliterans has been studied to date. The diagnosis of this disease was based on a typical history of intermittent claudication, the finding of reduction in or absence of arterial pulsations in the extremities, and the presence of evidence of arterial calcification on plain roentgenograms of the extremities, or evidence of arterial narrowing or occlusion on arteriograms, or roentgenographic evidence of both calcification and narrowing or occlusion.

Of the 105 patients included in the study, 41 were classified by history and physical examination as having "chronic" arteriosclerosis obliterans, their chief symptom being chronic intermittent claudication. Sixty-four patients presented a clinical picture of sudden arterial occlusion characterized by the acute onset of pain, pallor, weakness, numbness or coldness of an extremity, or a history of abrupt and significant shortening of their claudication distance, in addition to the findings of marked ischemia. No source of an arterial embolus was evident in any of the patients in the latter group. Data on age and sex as well as other pertinent clinical data are presented in Table 1.

METHODS OF STUDY

The laboratory methods used included: [1] the plasma clot (recalcification) time (5); [2] the

TABLE 1. Clinical Features in 105 Patients with Arteriosclerosis Obliterans

Clinical Type	Sex		Age Range, Years	Patients with Evidence of:	
	Male	Female		Coronary Disease	Diabetes
Chronic arteriosclerosis obliterans	36	5	34-80	5	7
Acute arterial occlusion	54	10	36-85	7	7

one-stage prothrombin time of Quick (6) as modified locally (7); [3] the thromboplastin-generation test of Biggs and Douglas (8), modification of Duckert, Flückiger, Isenschmid, Matter, Vogel-Meng, and Koller (9), with additional local modification (10, 11); and [4] the serum-cholesterol method of Zak (12).

TABLE 2. Typical, Normal Thromboplastin Generation Test*

Incubation, Minutes	Clotting Time, Seconds		
	CP† CS	PP PS	PP CS
1	44	45	46
3	34	26	36
5	20	17	20
7	12	14	11
8	9.8	9.6	9.4
9	8.4	8.6	8.8
10	8.4	8.4	8.4
11	1:2 = 19‡	1:2 = 19‡	9.0
	1:3 = 27‡	1:3 = 29‡	
12	9.0	9.2	

* The shortest clot times, 8.4 seconds, were reached in 9 to 10 minutes for both the control and the patient.

† CP = control plasma; PP = patient's plasma (both are adsorbed with barium sulfate and diluted 1:25 with buffered saline solution); CS = control serum; PS = patient's serum (both are aged 24 hours at 24° C and diluted 1:10 with buffered saline solution). Soybean phosphatide was used as platelet substitute.

‡ Incubation mixture was diluted twofold (1:2) and threefold (1:3) with 0.9% saline, yielding clot times of 21 and 35 seconds respectively. These values were obtained for purposes of quantitation. (Reproduced from SPITTEL, J. A., JR., PASCUZZI, C. A., THOMPSON, J. H., JR., and OWEN, C. A., JR.: Acceleration of early stages of coagulation in certain patients with occlusive arterial or venous diseases: use of a modified thromboplastin generation test to evaluate clot acceleration. *Proc. Mayo Clin.* 35: 37, 1960.)

Normal values for the aforementioned tests used are: [1] plasma clot time, 90 to 110 seconds; [2] prothrombin time, 17 to 19 seconds; [3] thromboplastin-generation test, shortest clot time (eight to 11 seconds) occurring at seven to 11 minutes of incubation (Table 2), and "retarded thromboplastin-generation test," normal being a clot time of 13 to 16 seconds in 11 to 13 minutes of incubation (13); and [4] serum-cholesterol test, 150 to 250 mg per 100 ml.

In addition, platelet counts were obtained in 37 of the 105 patients. These were made by the direct citrate method, the normal range being 125,000 to 300,000/mm³ of blood.

FINDINGS

A TYPICAL CASE

The protocol of the thromboplastin-generation test of a 54-year-old man with arteriosclerosis who sustained an acute thrombotic aortic occlusion (Figure 1) is shown in Table 3. This is typical of accelerated thromboplastin generation. When his plasma was diluted conventionally (1:25), the end point (shortest clot time) was reached two to three minutes sooner than in the control. The use of 1:50 dilutions of the control and the patient's plasma magnified the acceleration present in the system containing the patient's plasma. Also, the yield of thromboplastin was greater than in the control when the patient's plasma was diluted 1:50; this was not obvious at the 1:25 dilution.

FINDINGS IN THE GROUP

The frequency with which accelerated thromboplastin generation was encountered in the patients with chronic arteriosclerosis obliterans was markedly different from the frequency in the patients who had sustained an acute arterial occlusion (Table 4). The finding of accelerated thromboplastin generation in 70% of the patients who had had an acute arterial occlusion certainly tempts one to speculate that the development of such acceleration was related to the acute arterial occlusion; this is particularly true in view of the infrequency of acceleration of thromboplastin generation (12%) in the patients with chronic arteriosclerosis obliterans.

From examination of plasma clot times, platelet counts, and cholesterol determinations in Table 4, it is not possible to relate acceleration of thromboplastin generation to the results of any of these tests. The one-stage prothrombin time was normal in all patients who had received no anticoagulant drugs; no abnormally short prothrombin time (that is, less than 17 seconds) was observed in any of the 105 patients.

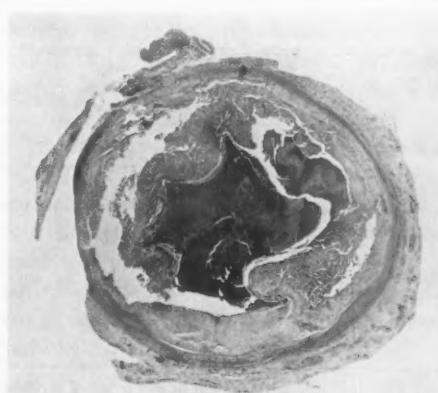


FIGURE 1. Cross section of abdominal aorta of a 54-year-old man whose clinical picture was compatible with acute aortic occlusion occurring two and one-half weeks previously. Atheromatous changes as well as complete occlusion of lumen by organizing thrombus are evident (hematoxylin and eosin; $\times 5$).

Gangrene of part or all of an extremity was present in only four of the patients with accelerated thromboplastin generation. One patient had accelerated thromboplastin generation one day after an acute arterial occlusion, while three and one-half weeks later his thromboplastin generation was normal despite the presence of gan-

TABLE 3. Example of Acceleration in the Thromboplastin Generation Test

Incubation, Minutes	Clotting Time, Seconds					
	CP* CS	PP PS	PP CS†	CP PS	CP 1:50† CS 1:10	PP 1:50† CS 1:10
1	65	65	76	78	70	70
3	50	47	46	72	57	38
5	32	31	14.4	41	49	13.4
7	20	11.8	8.0		37.6	10.2
8	11.6	8.8	7.8	15	29	10
9	9.6	8.2	9.2	12.4	21	10
10	8.4	8.8		11.2	16	9.2
11	8.8	1:2 = 20‡		9.0	15	9.8
		1:3 = 35‡				
12	1:2 = 25‡			9.6	15.4	10.2
13	1:3 = 35‡				14.4	
14					16.0	

* CP = control plasma; CS = control serum; PP = patient's plasma; PS = patient's serum. Plasma diluted 1:25 and serum diluted 1:10 with buffered saline solution.

† Plasma diluted 1:50 with buffered saline solution.

‡ Dilutions of incubation mixture with 0.9% saline solution.

TABLE 4. Results of Coagulation Studies in 105 Patients with Arteriosclerosis Obliterans

Clinical Type	Result	Thromboplastin-Generation Test		Range of Values		
		Patients*	Per Cent	Plasma Clot Time, Seconds	Platelets/mm ³	Cholesterol, mg/100 ml
Chronic arteriosclerosis obliterans	Normal	36	87.8	57-138	146,000-283,000	136-356
	Acceleration	5	12.2	55-99	217,000†	177-228
Acute arterial occlusion	Normal	19	29.7	52-109	119,000-310,000	143-444
	Acceleration	45	70.3	62-94	134,000-662,000	140-305

* No sex differential noted in incidence of accelerated thromboplastin generation.

† Only one of these five patients had a platelet count.

grene of the leg. Thus, gangrene does not appear to be the cause of accelerated thromboplastin generation.

Seventeen of the 45 patients with accelerated thromboplastin generation associated with an acute arterial occlusion were studied between one day and one year after an operation, while the other 28 were studied preoperatively. In one patient the acceleration of thromboplastin generation was the same after two and one-half months as it had been on the fourth postoperative day, and in two patients the acceleration was of the same degree postoperatively as it had been preoperatively. The postoperative state does not, therefore, appear to account for the finding of accelerated thromboplastin generation.

SERIAL STUDIES

Serial studies of thromboplastin generation have been made in ten patients. In three patients the acceleration disappeared in three and one-half weeks to three months, while in six patients it was unchanged over periods of two and one-half to six months. In fact, in the tenth patient serial studies over a three and one-half-year period have shown no change in the accelerated thromboplastin generation, even though continuous therapy with bishydroxycoumarin has been given during this period.

In none of the 105 patients was any acceleration of thromboplastin generation observed in the serum. In every case of accelerated thromboplastin generation the acceleration was demonstrable only in the plasma reagent (that is, barium sulfate-adsorbed plasma) of the thromboplastin-generation test.

COMMENT

During normal blood coagulation the generation of plasma thromboplastin takes longer than all the subsequent steps combined. Thus, if acceleration of any of the phases of blood coagulation was likely to account for hypercoagulability, it seemed logical to us, as well as to others (14, 15), for the acceleration to occur in the earliest phases of clotting, that is, in the generation of plasma thromboplastin. Accordingly, the thromboplastin-generation test, designed to measure the rate of formation and the amount of thromboplastin formed under standardized conditions, was employed in this study of the coagulation mechanism of patients with arteriosclerosis obliterans.

In order to increase the likelihood of detecting any clot acceleration present, we have modified ("retarded") the thromboplastin-generation test by increasing the dilution of the plasma reagent. Our use and interpretation of the "retarded" throm-

boplastin-generation test are described in detail in a preliminary report (11).

The finding of accelerated thromboplastin generation in 70% of patients with acute arterial occlusion complicating arteriosclerosis obliterans confirms the suspicion of earlier investigators that some change in blood coagulability is associated with the terminal thrombotic occlusion of the arteriosclerotic artery.

Persistence of the acceleration of thromboplastin generation for as long as three and one-half years in one patient and its disappearance in three and one-half weeks in another support the concept that the hypercoagulable state can be variable and brief, or prolonged. This phasic nature of accelerated thromboplastin generation may in itself explain our failure to demonstrate accelerated clotting in approximately a third of the 64 patients with acute arterial occlusion. Alternative explanations that must be considered, however, are that our present method, the "retarded" thromboplastin-generation test, may still be relatively insensitive, and that thrombosis may be caused by mechanisms other than accelerated thromboplastin generation in some patients.

The frequency with which accelerated clotting is associated with acute arterial occlusion quite naturally raises the question of why accelerated clotting was detected in five patients who were believed to have chronic arteriosclerosis obliterans. In none of these five patients was there good evidence for an acute arterial occlusion. In one of them, a 36-year-old man, intermittent claudication and an ischemic ulcer had appeared rather abruptly after a surgical procedure; he may have sustained an acute arterial occlusion, but the history and findings were not sufficiently typical to permit his inclusion in the group with acute arterial occlusion. As mentioned, in the other four patients there was no history even suggestive of acute arterial occlusion. If our concept of accelerated clotting and its rela-

tion to acute arterial occlusion is correct, our findings may prognosticate an acute occlusion in the future. Only time will clarify this latter point.

We have been impressed in our studies by the observation that the acceleration of thromboplastin formation is more important in hypercoagulable states than is the yield of thromboplastin. Nonetheless, those patients showing accelerated thromboplastin generation usually also show a greater yield of thromboplastin.

Since patients with acute arterial occlusion were studied after their thrombotic episode had occurred, the possibility arises that acceleration of thromboplastin generation is the result rather than the cause of the thrombosis. That it is the result does not seem likely, however, since the accelerated clotting has persisted for as long as three and one-half years after an arterial occlusion in one patient in spite of continuous anticoagulant therapy with bis-hydroxycoumarin. Furthermore, the cause of the accelerated thromboplastin generation is an excess of a coagulation activity present in the plasma of normal persons.

Studies reported in detail elsewhere (13) have demonstrated that the substance responsible for the acceleration of thromboplastin generation in these thrombotic patients is a protein, electrophoretically a beta-globulin, that is not adsorbed by barium sulfate, and that disappears with clotting. While it bears some resemblance to antihemophilic globulin superficially, extensive studies have shown this accelerator to be distinct and different from antihemophilic globulin as well as from all other previously described clotting factors (13).

Furthermore, while the accelerator of thromboplastin generation is present in normal plasma, it is present in marked excess in the plasma of patients showing accelerated thromboplastin generation. The unique characteristic of this accelerator, by which it is adsorbed by aluminum hydrox-

ide but not by barium sulfate, may explain the reason for the failure of the standard thromboplastin-generation test (which utilizes aluminum hydroxide to adsorb the plasmatic reagent) to detect its presence.

The accelerator of thromboplastin generation appears to be active in the initial phases of clotting, that is, in the formation of plasma thromboplastin, since its activity is demonstrated by the thromboplastin-generation test, but not by the prothrombin-time test of Quick. We have tentatively named the accelerating activity "thromboplastin-generation accelerator," abbreviated TGA.

The presence of thromboplastin-generation accelerator in the plasma rather than in the serum is a fundamental characteristic which distinguishes it from the serum factor (STA) described by Wessler and Reimer (16) and from the activation product described by Waaler (17), both of which appear to be related in some way to Hageman factor and plasma thromboplastin antecedent (PTA). Differences in techniques of study, of course, raise the possibility that thromboplastin-generation accelerator, serum thrombotic accelerator, and activation product are related intermediates in the earliest phases of clotting. Clarification of this point will have to await further elucidation of the intermediate phases of the formation of plasma thromboplastin.

In an interesting study of atherosclerotic and normal persons, Mustard (18) reported that persons with "atherosclerotic vessel disease" showed hypercoagulability of the blood when the results of several clotting tests, including a standard thromboplastin-generation test, were compared statistically. Although he concluded from his study that the difference was due to excessive levels of Christmas factor (PTC), it may be that he was observing the same phenomenon that we are reporting. For the adsorption of the plasmatic reagent he utilized aluminum hydroxide rather than barium sulfate.

The association of excessive activity of

the accelerator of thromboplastin generation with the occurrence of acute arterial occlusion in arteriosclerosis obliterans immediately raises the question of the effect of anticoagulant drugs on this accelerator. The results of serial thromboplastin-generation tests performed before and during the course of coumarin anticoagulant therapy in ten patients have shown that coumarin drugs do not affect this accelerator. Despite the continued excess activity of the accelerator in the plasma, it is our impression from limited clinical experience that coumarin anticoagulant therapy does produce a net protective effect against thrombosis by its known depressant action on other clotting factors, namely factor IX (Christmas factor), factor VII (stable factor), factor X (Stuart-Prower factor), and prothrombin.

SUMMARY

By means of a "retarded" thromboplastin-generation test, acceleration of thromboplastin generation has been demonstrated in 70% of 64 patients with acute arterial occlusion complicating arteriosclerosis obliterans. This hypercoagulable state is produced by excess clotting activity which appears to be a previously unrecognized accelerator of thromboplastin generation. The excessive activity of this accelerator may be a temporary phenomenon or may persist for as long as three years. Coumarin anticoagulant drugs do not appear to exert any direct effect on the activity of this accelerator.

SUMARIO IN INTERLINGUA

Per medio de un "relentate" test del generacion de thromboplastina, le ocurrentia de un acceleratione de ille generacion de thromboplastina esseva demonstrate in 70% de un gruppo de 64 pacientes con acute occlusion arterial, presente como complicacion de arteriosclerosis obliterante. Iste stato de hypercoagulabilitate es producite per un excessive activitate coagulatori que apparentemente es un previamente non recognoscite accelerator del generacion de thromboplastina. Le excesso de activitate de iste

accelerator pote esser un phänomeno temporari, sed illo etiam pote persistir durante periodos de usque a tres annos. Il pare que anticoagulantes coumarinic non exerce un efecto directe super le activitate de iste accelerator.

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Antimalarial Therapy of Lupus Erythematosus

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THE TREATMENT OF LUPUS ERYTHEMATOSUS with antimalarial compounds has been pursued for almost a decade in this country. In that time, many clinicians have been impressed by the therapeutic efficacy of these drugs. Yet, only one long-term follow-up study (1) is available on which to base a judgment of the value of these drugs. We wish to report data on the results of treatment of lupus erythematosus, both discoid and systemic varieties, seen at the Mayo Clinic, in cases in which quinacrine hydrochloride (Atabrine) therapy was started in 1952 or early in 1953. Early results of treatment in some of these cases were reported by Kierland, Brunsting, and O'Leary (2). Data to be presented indicate what has been accomplished in terms of cures, remissions, relapses, and toxic reactions.

METHOD

The records of 70 patients seen at the Clinic in 1952 and 1953 who were given a diagnosis of lupus erythematosus and who were treated with quinacrine hydrochloride (Atabrine) were reviewed. Concerning those patients not seen at the Clinic periodically for follow-up, pertinent data were obtained by sending questionnaires to the patient, his physician, or both. One patient could not be traced, and the origi-

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nal diagnosis given to two patients was thought to be in error. Our observations, therefore, are based on 67 patients for whom there was adequate follow-up. This group was composed of five patients with subacute systemic lupus erythematosus, seven with chronic generalized discoid lupus erythematosus, and 55 with chronic localized discoid lupus erythematosus. The follow-up period for 58 of these patients was five years or more. Nine died in less than five years: three of lupus erythematosus, three of carcinoma, one of a cerebrovascular accident, and two of unknown causes. This group was assessed in terms of clinical response of lesions to therapy.

Biopsies were done on the lesions when indicated, and 24 such lesions were consistent histologically with the diagnosis of lupus erythematosus. Routine laboratory work, including leukocyte counts, differential counts, tests for hemoglobin, roentgenograms of the thorax, and urinalysis, was carried out on all patients. Flocculation tests for syphilis, lupus erythematosus clot tests, serum protein studies, platelet count, determination of sedimentation rate, and other studies were obtained when indicated.

Treatment of all patients with quinacrine hydrochloride (Atabrine) was begun with doses of 200 to 300 mg daily for seven days, then 100 to 200 mg daily for one to two weeks, then 100 mg daily as a maintenance dose. All patients were instructed to avoid exposure to the sun. Many used a sun-protective cream, and some were treated on one or more occasions with carbon dioxide locally. Twenty-four patients were treated with quinacrine alone; another 26 received first quinacrine, then chloroquine (Aralen). The remaining 17 patients received quinacrine and later chloroquine, hydroxychloroquine (Plaquenil), amodiaquin (Camoquin) or a combination of the first three (Triquin).

Multiple uncontrolled variables such as dosage, regularity in administration, amount of exposure to the sun, and personal factors exist

and, therefore, only general classifications can be used in evaluating the therapeutic response. The four categories used seem functional and realistic: group A, remissions of five years or more without relapse, in whom scars remain but there is no activity in any of the lesions; group B, three to five-year remission without relapse; group C, definite improvement, relapses common; and group D, minimal to no improvement.

RESULTS

Five patients comprised group A and two group B. Fifty of the patients were placed into group C and ten belonged in group D. The age of onset, duration of lesions, age when treatment was begun, and sex did not differ significantly in the groups. No sex differences were noted in terms of response in any group.

GROUPS A AND B

These groups were composed of six patients with discoid lupus erythematosus and one with subacute systemic lupus erythematosus. Five of the seven were females and five of the seven had had previous gold and bismuth therapy. The patient with subacute systemic lupus had been treated elsewhere with ACTH intramuscularly. We gave no steroids to this group of patients during antimalarial therapy. All patients showed marked improvement on treatment with quinacrine in four to eight weeks. One patient, who took quinacrine for only ten weeks and stopped when the lesions were inactive, has gone seven years without relapse. The others required four months to four years of total therapy and then experienced three to five-year remissions. Five of the group required only quinacrine; chloroquine was later utilized for the remaining two.

Case 1: A white male student who presented with subacute systemic lupus erythematosus and whose problem was resolved with therapy was seen at the age of 22 years. He had had fever, arthralgia, malaise, loss of weight, and a cutaneous eruption for one year. Positive laboratory findings included albuminuria, hematuria, ane-

mia, leukopenia, elevated sedimentation rate, and a positive lupus erythematosus clot. He was sent home to rest in bed, to take 400 mg of quinacrine hydrochloride daily, and to use supportive care. He remained in bed for four months, rested for 15 more months and had a total of three years of continuous therapy with quinacrine. Seen then, he was asymptomatic and all laboratory findings had returned to normal. He returned to college and has now gone five years without therapy and without relapse, and is leading a normal life as an architect.

Although it is tempting to consider patients in groups A and B as potentially cured, it is well to recognize that experience does not justify this conclusion. One 52-year-old woman with chronic discoid lupus erythematosus was treated with quinacrine for four months. She then had a six-year remission only to suffer a subsequent relapse.

GROUP C

The 48 patients with discoid lupus erythematosus and the two with systemic lupus erythematosus in this group responded favorably to the first course of quinacrine. Most of them had marked resolution within two to 12 weeks of therapy. Forty-eight had at least one relapse after initial clearing and cessation of treatment with quinacrine. Forty-five had at least two relapses, and the majority had multiple relapses after quinacrine or other antimalarial therapy was stopped. The frequency and severity of the relapses and the rapidity of their onsets after cessation of therapy were not related to the duration of the initial course of therapy. The length of the initial course of quinacrine varied from two weeks to 25 months, and one patient has taken quinacrine continuously for seven years. In some cases quinacrine seemed progressively less effective in controlling relapses until it was of no value. Increasing the dosage in such cases was without effect.

Treatment with chloroquine was instituted in 36 cases because of lack of response to quinacrine therapy, high relapse rate,

onset of side reactions, or because of the availability of chloroquine. The majority of these patients responded initially to chloroquine as they had to quinacrine, but the relapse rate was approximately the same. The patients tolerated chloroquine better than quinacrine. For some of these patients hydroxychloroquine, amodiaquin, and a combination of quinacrine, chloroquine and hydroxychloroquine (Triquin) were tried. Some later returned to a previously ineffective medicament, such as quinacrine, and obtained a satisfactory response. One patient unresponsive to quinacrine, chloroquine, and hydroxychloroquine, when given separately, responded nicely to all three in combination (Triquin) and then later to amodiaquin. Continued treatment for varying periods of time after the skin lesions cleared seemed to have no protective effect against relapses. Lesions of some patients became active while they were receiving maintenance doses; increasing the dose did not help. Substitution of another antimalarial was often effective. It is not possible to draw any conclusions about the relative effectiveness of hydroxychloroquine, amodiaquin, or Triquin. In many instances they were effective when quinacrine and chloroquine no longer seemed so.

GROUP D

The ten patients classified as having treatment failures included eight with discoid lupus erythematosus and two with the systemic form. Nothing distinguished this group of patients from those who responded well to therapy. The number and location of lesions, the duration of lesions prior to treatment, age, and sex were factors of little or no significance in determining this group. In general, these patients had had minimal therapy prior to antimalarial treatment. Two had had prior gold therapy and one had had bismuth. Regardless of the dose used or the duration of treatment,

these patients showed minimal or no response to quinacrine. One patient whose condition was completely unresponsive to six months of treatment with quinacrine was controlled by chloroquine phosphate for four years until his death from adenocarcinoma of the rectum. For two other patients whose lesions were unresponsive to quinacrine therapy chloroquine was tried and in both instances only a fair response was obtained.

TOXIC REACTIONS

Toxic reactions were more numerous and severe with quinacrine therapy than with chloroquine. These reactions included a bullous erythema multiform-like reaction, a lichenoid dermatitis, and a generalized papulosquamous eruption. The most frequent side effects were gastrointestinal upsets including indigestion, anorexia, nausea, vomiting, and diarrhea with cramps. These occurred in ten patients. In five patients, bluish discoloration of the nail beds was noted. Two patients mentioned excessive dreaming and one patient had pruritis of the face, one had an hysterical reaction with syncope, and one had melanosis.

One patient was treated intermittently with chloroquine for several years. Seven years after initiation of treatment corneal opacities consistent with chloroquine deposits were noted. Nausea occurred in two patients; diarrhea, headache, and vertigo in two; a maculopapular eruption of the hands in one; and moderate leukopenia in one.

One patient taking amodiaquin complained of arthralgia, myalgia, stiff neck, and vertigo, and another patient had moderate leukopenia. Triquin caused nausea in one patient and hydroxychloroquine caused a "nervous shake" sensation in one.

Toxic or side reactions to one drug did not preclude the use of other drugs in any one of these cases.

COMMENT

It is readily apparent that one cannot speak of "cure" of lupus erythematosus with antimarial medication. In almost all of the cases in which the response was satisfactory a flare-up of the process developed subsequently. Even a five-year cure is not absolute, for one patient had a relapse after a clinical remission of seven years' duration following a single course of therapy. Whatever their mode of action, the antimarial drugs have only a suppressive effect on this disease.

The majority of the patients studied responded well to treatment only to have an exacerbation of the process later. Consequently it appears axiomatic that the typical patient with lupus erythematosus will require intermittent antimarial therapy for years. We now have patients who have been treated repeatedly in this manner for nine years. This is further evidence of the suppressive rather than the curative effect of such medication. It is also apparent that when a physician begins antimarial therapy for lupus erythematosus, he should realize that long-term administration may be necessary.

Some antimarials, of course, will work better than others for certain patients. No factors were elicited in the course of our study which could be used as criteria aiding the physician to predict which patient might respond favorably to any given antimarial. The choice must be made on the basis of clinical trial and close observation for any side effects and toxic reaction. Although hydroxychloroquine and chloroquine are commonly considered to be the drugs of choice, it must be recognized that some patients will respond only to quinacrine (Atabrine) and amodiaquin.

Not all antimarial compounds are useful in lupus erythematosus. Clinical experiences have shown that only the 4-aminoquinoline and related compounds are satisfactory. All effective compounds have a

structural similarity. Another aminoquinoline (Propaqueine) has been used in six cases of discoid lupus with only minimal suppressive effect. It should be possible to formulate a more suppressive but less toxic agent with basic similarity to the 4-aminoquinoline compounds. Since patients need such treatment for long periods, we urge further search for such drugs.

The antimarial compounds are occasionally toxic in the dosage range given for antiplasmodial effect. The doses usually used for treatment of lupus erythematosus are two to three times the usual suppressive antiplasmodial dose. The number and severity of toxic reactions are accordingly increased, and both acute and chronic hematopoietic, gastrointestinal, central nervous system, and epidermal toxic effects are seen. These effects limit the program for the individual patient. Since the patient will undoubtedly need treatment for a long time, the medication used must be well tolerated by his system and must be given in the smallest possible dose from the beginning of treatment. In most instances, it seems desirable to use small doses and accomplish the effect slowly rather than to use large doses to obtain a dramatic clinical effect. Attention should be called to the acute deaths reported in children following accidental chloroquine ingestion (3). These drugs should be labeled so that adults recognize this problem.

The results of treatment of systemic lupus erythematosus with antimarial medicaments can be dramatic as in Case 1. On several occasions we have seen similar effects, and we consider antimarial drugs to be a major factor in the therapeutic armamentarium against systemic lupus erythematosus. The disease process is so severe that it is usually possible to accept the added risk of toxicity from this medication if it has a reasonable chance of being effective. We have found it principally useful in the treatment of patients receiving

steroids. The addition of an antimarial drug to the program of such patients usually makes possible smaller dosage of steroids and more rapid reduction of the dosage.

SUMMARY

A long-term follow-up study is presented of 67 patients with discoid and systemic lupus erythematosus who were seen at the Mayo Clinic, and who were treated originally with quinacrine (Atabrine). Of these patients, 58 have been followed for five or more years. Both systemic and discoid varieties of lupus erythematosus were benefited by antimarial therapy.

Seven of the 67 patients had complete remissions for three years or more without further therapy. Fifty of the 67 patients responded nicely to treatment with quinacrine, but had multiple relapses and required multiple courses of therapy. The remaining ten patients showed little or no response to treatment.

The action of antimarial compounds in suppressing this process is undisputed; however, the high relapse rate of lupus erythematosus after antimarial therapy is disappointing and the necessity for continued administration of these compounds for years is deplored. It is hoped that a related drug that is less toxic and more effective will be found.

SUMARIO IN INTERLINGUA

Es presentate un studio de anamnese a longe vista in 67 patientes con lupus erythematose discoide e systemic qui esseva vidite al Clinica Mayo e in qui le tractamento original habeva esse cursos de quinacrina (Atabrina). Inter iste patientes, 58 esseva observate durante 5 annos o plus. Tanto casos systemic como etiam casos discoide de lupus erythematose derivava beneficios ab le therapia antimarial.

Septe del 67 patientes habeva complete remissiones de un duration de 3 annos o plus sin therapia additional. Cinquanta del 67 respondeva satisfacentemente al cursos de quinacrina sed habeva multiple recidivas e requireva multiple cursos del therapia. In le remanente 10 patientes, le tractamento evocava pauc o nulle responsa.

Le action supprimente iste processo, exercite per compositos antimarial, non es disputate. Tamen, le alte incidentia de recidivas de lupus erythematose post therapia antimarial es disappunctante. Le necessitate de und continue administration de iste compositos durante un numero de annos es a depolar. Le spero es exprimite que un droga asfin va esser trovate que es minus toxic e plus efficace.

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The Incidence of Immediately Reacting Allergy Skin Tests in a "Normal" Adult Population

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THE INCIDENCE OF IMMEDIATE wheal and flare skin reactions* among allergic and nonallergic individuals continues to evoke considerable discussion and is, as yet, far from settled. Clinical experience has shown that positive skin reactions are found very frequently among patients with allergic rhinitis, bronchial asthma, and infantile eczema. A recent study stated, in addition, "it is established that many *normal*† people show a proportion of positive skin reactions to allergenic extracts" (1). As evidence for this assertion the work of Rackemann and Simon (2), Grow and Herman (3), and Herxheimer, McInvoy, Sutton, Utidjian, and Utidjian (4) was cited, all of whom had reported that about 50% of nonallergic individuals had some positive skin reactions. Pearson (5), on the other hand, found the incidence of positive skin reactions in nonallergic individuals to be under 5%. The clinical impression of practicing allergists has also been that positive skin tests in nonallergic patients are rare (6, 7).

These discrepancies warranted further study of the incidence of skin reactions produced by commonly used allergenic extracts.

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* In this paper reactions of the immediate wheal and flare variety will be referred to as positive skin tests. The term "allergy" will indicate an acquired specific alteration in the capacity of an individual to react, presumably mediated by the presence of antibody.

† Emphasis ours.

MATERIALS AND METHODS

Our subjects included hospitalized patients, hospital staff, employees, and medical and dental students. The relative proportion of each and their age range are shown in Table 1. All but two were white. The 100 individuals in the table had no personal or family history of allergy. They were selected from more than 300 persons who were questioned in detail, following a form which included both direct and indirect questions about the presence of possible allergy (Table 2). Seventy members of a dental school class were included in this larger group, only 18, or 26%, of whom were found to have no personal or family history of allergy. In questioning, words such as "catarrh," "bronchial," and "sinus" were freely used. The decision whether a subject was suitable for inclusion in the nonallergic group was made before testing. In four subjects, however, a personal or family history of allergy was recalled after testing was completed, and these individuals were dropped from the nonallergic group. Since it was not always certain whether a given symptom obtained by history was really allergic, all doubtful cases were also excluded from the nonallergic group.

Two additional groups of subjects were also collected, partly from the dental school class already mentioned, and the remainder from individuals discovered in the search for nonallergic subjects. One group comprised 40 persons, mainly from the dental class and including only those with a definite history of seasonal hay fever and

TABLE 1. Composition of 100 Nonallergic Subjects

Patients				Staff and Students		
Male	Female			Male	Female	Total
33	21			27	19	100
Ages Number of subjects	16-20 8	21-30 30	31-40 17	41-50 14	51-60 13	Over 60 18

TABLE 2. Form Followed in Recording History

History

1. Infancy: Did you have
- (a) Croup
 - (b) Colic
 - (c) Eczema
 - (d) Intolerance to food (milk substitute)
 - (e) Hives
 - (f) Asthma
2. Childhood: Did you have
- (a) Swelling of the lips or eyes
 - (b) Hospitalization for "bronchiolitis"
 - (c) Wheezing with colds
 - (d) Frequent "colds" (or stuffy nose)
 - (e) Time lost from school. Why?
 - (f) More than one tonsillectomy and adenoidectomy
 - (g) Nosebleeds
 - (h) Itching of nose, eyes, throat, ears, palate
 - (i) Recurrent or paroxysmal sneezing
 - (j) Intolerance to pets due to allergy. Explain.
 - (k) Hay Fever—spring
- fall
summer
winter
- (l) Asthma—spring
- fall
summer
winter
- (m) Reactions to drugs. Which?
3. Adulthood: Did you have
- (a) Sinus trouble. Define.
 - (b) Stuffy, blocked nose or mouth breathing
 - (c) Indigestion associated with eating specific food
 - (d) Have you ever been to an allergist?
 - (e) Have you ever been skin tested?

Family history:

Did your mother, father, brother, sister, children ever have any of the above symptoms?
Did they ever have asthma, perennial rhinitis, hives, hay fever, "catarrh"?

asthma. The other was composed of 42 persons with a family history of allergy only. Although these groups were not matched,

they were tested with the same technique and by the same criteria as the nonallergic subjects.

The nine allergenic extracts used for skin tests in this investigation were obtained from standard commercial sources.* They included plantain, 1/10; ragweed, 1/10; timothy, 1/10; alternaria, 1/10; birch, 1/10; oak, 1/10; house dust, 1/40; feathers, 10,000 protein nitrogen units; and cat, 1,000 protein nitrogen units, and were chosen because we felt they were the inhalant antigens most commonly reacted to in this area. The extracts were diluted with phenolized saline, refrigerated, and tested periodically for potency on known allergic individuals. In addition, we compared the commercial extracts with those made in our laboratory for use in the Allergy Clinic by a small number of patients from time to time throughout the six months of the study, and found the skin reactions similar.

The scratch tests were performed with a surgical straight needle with just enough pressure to abrade the epithelium. Each subject was checked beforehand to make certain he was taking no drug that might interfere with skin reactivity. The tests were considered positive when there was a wheal and flare reaction definitely larger than the other scratch tests. The scratch test is difficult to standardize further. It is generally employed initially on a patient because systemic reactions are very rare with its use.

In all cases where the scratch test was negative or doubtful, an endodermal test was performed. The dilutions employed were plantain, 1/1,000; ragweed, 1/1000; timothy, 1/1,000; alternaria, 1/500; birch, 1/1,000; oak, 1/1,000; house dust, 1/4,000; feathers, 1,000 protein nitrogen units; and cat, 100 protein nitrogen units, with a saline control. A No. 26, one-quarter inch needle was used with just enough extract injected to raise a barely visible wheal, not exceeding 0.02 millimeter. A test was recorded as being definitely positive when the wheal reaction was at least 10 milli-

TABLE 3. Positive Reactions in Nonallergic Group

Status	Age	Sex	Scratch	Endodermal	Com-
					bined
1. Student	27	M	Timothy	Ragweed	1
2. Student	23	M	Ragweed	Dust	1
3. Student	20	F	—	Ragweed	1
4. Patient	46	M	—	Dust	1
5. Patient	72	F	Ragweed	Dust	1
6. Patient	44	M	—	Dust	1
7. Staff	33	M	—	Dust	1
8. Staff	30	M	—	Dust	1
9. Staff	42	F	Ragweed	Dust	1
Total subjects reacting			4	9	9

meters larger than the control (+++), or less than 10 millimeters with pseudopods (++) . Five to 10 millimeter reactions were recorded but considered doubtful when no pseudopods were present (+). Reactions smaller than 5 millimeters were read as negative.

RESULTS

The number and types of positive reactions (++ or greater) in our subjects are recorded in Table 3. Five (5%) of the subjects were positive to at least one scratch test, and nine (9%) had positive results when the scratch tests were supplemented by endodermal tests. It is of interest that there were only four doubtful (+) reactions by our criteria. Three of these were to house dust and one was to feathers. Of the five definite positive tests by the scratch method, three (60%) were to ragweed. Of the ten positive endodermal reactions (in nine subjects), seven (77%) were to house dust.

DISCUSSION

It has been stated frequently that the mere presence of a positive skin reaction to some allergenic extract does not necessarily mean that the reaction is clinically significant. It has also been observed frequently that patients with isolated seasonal symptoms (for example, to ragweed) will

* House dust from Endo Laboratories Inc., Richmond Hill, N. Y. All other extracts from Center Laboratories, Inc., Port Washington, N. Y.

TABLE 4. Positive Reactors Among
40 Allergic Subjects

	Number Reacting to		
	Scratch	Endodermal	Combined
Pollens and alternaria	30 (75%)	4	34 (85%)
Dust	5 (12.5%)	18	23 (57.5%)
Feathers	3 (7.5%)	12	15 (37.5%)
Cat	2 (5%)	1	3 (7.5%)
Total number of subjects reacting	33 (82%)	36 (90%)	

have positive skin tests to many other allergenic extracts as well. Finally, there is a certain small percentage of patients with striking seasonal allergic symptoms who do not react to any skin tests. It would be most surprising, however, to find that there was little or no difference in the over-all incidence of skin reactivity when allergic patients are compared with nonallergic controls. Such a finding, moreover, could not help but destroy confidence in the diagnostic value of the skin test.

It was reassuring, therefore, to find that with our extracts and criteria, the incidence of positive skin reactions was quite low. When the same extracts were tested in the 40 individuals with a definite seasonal history of rhinitis, asthma, or both, 33 (82%) reacted to one or more scratch tests, and three additional patients were positive when tested endodermally, making a total of 36 (90%) reactors (Table 4). This represented an incidence of reaction about nine times as great in the allergic subjects.

When the results of our study are compared with those in which a 50% incidence of positive reactions was obtained, certain differences in selection of subjects, standardization of extracts, and recording of results are apparent. Of these differences, selection of subjects is probably the most important. The crux of the problem is whether a "normal" or nonallergic individual is defined as one without any obvious allergic symptoms, or as one who is

completely free from all personal or family history of definite or possible allergy. In evaluating subjects, a questionnaire history or a routine query about "allergy" is of doubtful value. Even a careful examination in a major teaching hospital where every admission is questioned about eczema, hives, hay fever, contact sensitivities, drug idiosyncrasies, and skin tests is not adequate. More than two-thirds of the patients surveyed on the basis of negative answers to these questions on their charts had to be dropped from our nonallergic group because of the discovery of a personal or family history of definite or possible allergy. It is reasonable to assume that some allergic persons might have been missed, even in our double-checked cases. Individuals vary greatly in their ability to remember details of their past health. The more obsessive-compulsive appear to forget nothing. It would be natural for anyone to overlook trivial symptoms, while still others tend to repress all unpleasant experiences.

Our population was, of course, highly selected, with a relatively large proportion of hospitalized patients and professional people. It was also overbalanced in the 21 through 30 age range; this group comprised 30% of our series, but only about 20% of the white population of the United States (8). Three of our positive reactors came from this age group. It has been suggested that sensitivity to skin tests might be highest before the age of 30 and decrease thereafter (5). Studies by Wheeler indicated that about 20% of a series of 245 medical and dental students who gave no personal or family history of allergy had positive 1:20 scratch tests to ragweed and grass extract, or both (9). However, the history was obtained by questionnaire. In our own small group of 36 subjects between the ages of 19 and 30, only four (11%) had positive reactions, a percentage only slightly higher than the group as a whole.

Subjects with positive family histories of allergy must be excluded from a study such

as ours or at least separated from the subjects with no such family history. Only in Pearson's study (5), were the percentages of positive intracutaneous reactions to extracts of feathers, horse dander, wheat, egg white, and horse serum albumin compared in subjects with allergy, those with no symptoms and a negative family history, and those with no symptoms and a positive family history. In the nonallergic group with no family history only 4% had positive reactions, but in asymptomatic subjects with a positive family history, the incidence rose to about 30%. Bray reported an incidence of 25% positive reactions in nonallergic members of allergic families (10). In our group of 42 persons who had a positive family history only (Table 5), 14 (33%) were positive to one or more scratch tests, and 21 (50%) had at least one positive reaction when endodermal tests were also used.

In Grow and Herman's study (3), the 50% incidence of positive reactions was found in a group "most members of (which) came from families in which there was asthma, hay fever, and other allergic disease." The report by Rackemann and Simon (2) mentioned that several of their 60 subjects were later found to have personal or family histories of allergy. The most recent study reporting a high incidence of positive reactions, that of Herxheimer et al. (4), does not contain any information about the family history of their subjects.

The problem of standardization of extracts is a difficult one. Rackemann (11) has expressed the belief that the extracts used in his study in 1935 might have been more irritating than those in use today. Grow and Herman's study (3) was done in the following year. Herxheimer et al. (4) used the prick test (a modified scratch) and included late reactions in their results. It may be significant that over 30% of the patients in their series reacted to horse dander alone. This is a figure four times as high as the incidence of positive reactions in a large series of allergic patients (12).

TABLE 5. Positive Reactors among 42 Subjects with Positive Family History Only

	Number Reacting to		
	Scratch	Endodermal	Com-bined
Pollens and alternaria	12	11	19
Dust	3	7	10
Feathers	—	1	1
Cat	—	—	—
Total number of subjects reacting	14 (33%)		21 (50%)

Because there is no completely reliable chemical method of measuring the potency of extracts, comparison of different populations tested with different extracts of the same dilution or containing the same number of protein nitrogen units or the same milligrams per 100 milliliters of nitrogen, is not valid. An example of the risk of such a comparison was given by Efron (13) who described two house dust extracts, both with the same milligrams per 100 milliliters of nitrogen, and both producing positive reactions in about 80% of patients with a history suggesting dust sensitivity. In nonallergic controls, however, one extract gave 7.5% positives and the other 66.7% positive reactions. The only way in which one can even roughly compare two populations, therefore, is by "biologic standardization," that is, testing both allergic subjects and truly nonallergic controls. Subjects with positive family histories must be placed in a separate category. In this way our study is roughly comparable to Pearson's (5), even though his was done 25 years ago, in a different country, and using a different set of allergenic extracts.

Finally, the practice of recording "slight reactions" appears to have caused confusion. These are generally defined as very small flares and wheals less than 5 millimeters in diameter. Feinberg (12) has stated that such reactions "are likely to be fully as indicative of clinical allergy as a very

marked one." Our study does not disprove this contention, but the high over-all incidence of positive reactions in allergic subjects and those with a positive family history only, suggests to us that the diagnostic value of "slight reactions" is minimal. Furthermore, such reactions have a very poor reproducibility. Gottlieb, Stupniker, and Askovitz (14) have recently shown that when wheals greater than 5 millimeters in diameter were considered positive, there was a lack of uniformity of 13% in readings by different observers and a discrepancy of 27.2% when the test was repeated after six months. If, on the other hand, only wheals greater than 10 millimeters in diameter were considered positive, there was complete uniformity in the readings by different observers and a discrepancy of less than 5% after six months.

CONCLUSIONS

1. A study of the incidence of positive skin tests in 100 nonallergic subjects using nine allergenic extracts revealed one or more positive reactions in 9% of the subjects when the scratch and endodermal methods were combined and our criteria were used.

2. These results are compared with an incidence of one or more positive reactions in 90% of a group of allergic patients, and 50% of a group of nonallergic individuals who came from allergic families.

3. Reasons for the discrepancy between our findings and those in other studies suggesting a high incidence of positive reactions in nonallergic persons are discussed.

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SUMMARIO IN INTERLINGUA

Le incidentia de reaktiones immediate in tests cutanee pro allergia in individuos non-allergic (o "normal") remane un question indecise. Le opinion que iste genere de tests a resultado positive es multo frequente in tal personas es basate in plure investigationes in que approximativamente 50% de presumitamente non-allergic subjectos habeva al minus un cuti-reaction positive in le batteria de tests con extractos allergic.

Nos seligeva 100 non-allergic subjectos ab un population de studentes de medicina, patientes, e empleatos de hospital. Nulle de iste subjectos habeva antecedentes personal o familial de allergia. In plus, tests esseva effectuate in 40 personas con definite antecedentes personal de febre de feno o asthma o ambes e in 42 personas con solmente antecedentes familial de allergia. Novem extractos allergic esseva usate: de ambrosia, phleo de prato, alternaria, planagine, betula, querco, pulvere (de casa), plumas, e catto. Le technica de grattage esseva usate initialmente, sequite per tests endermic in omne caso de reaction negative o dubitose. Un reaction endermic esseva regardate como positive quando un vibile esseva presente de plus que 10 millimetres de diametro o de inter 5 e 10 millimetres con pseudopodios.

A base de nostre criterios, cinque del subjectos non-allergic (5%) habeva al minus un positive test de grattage, durante que novem (9%) reageva positivemente post le addition de tests endermic. In comparation con isto, 90% del patientes allergic habeva al minus un reaction positive e 50% del subjectos con antecedentes familial de allergia.

Nos opina que le plus importante ration per que previe investigatores reportava un alte incidentia de positive tests cutanee in subjectos "normal" esseva le inclusion de individuos con non-revelante antecedentes personal o familial de allergia.

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Scrub Typhus: A Follow-up Study

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SCRUB TYPHUS IS AN ACUTE FEBRILE ILLNESS caused by *Rickettsia tsutsugamushi*. It occurs widely throughout the southern Pacific islands and in southern Asia, especially in the southwest Pacific and in southeast Asia. The causative agent is transmitted by the bite of an infected mite. The disease is characterized by an eschar at the site of entrance of the infecting agent, an early generalized skin rash and, if unmodified by therapy, a prolonged high fever and evidence of widespread tissue damage. The most serious manifestations are myocarditis, meningoencephalitis, and pneumonitis. The untreated disease runs an acute and often severe course, with slow recovery. Before the advent of specific therapy (1) the case fatality ranged between 5 and 35%. Chloramphenicol and the tetracycline drugs have reduced this once-formidable disease to a brief illness of a few days. Although scrub typhus has long been known in the Far East and its etiology

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understood since 1924, it first involved large numbers of Occidentals in World War II when Allied armies are said to have sustained more than 18,000 cases (2); United States Army troops alone had about 5,440 cases with 284 deaths (3).

Although it is generally supposed that rickettsial diseases rarely have important sequelae, the profound changes observed in the acute and early convalescent stages of the disease as seen in the Twentieth General Hospital in Assam during World War II (4) suggested the desirability of further inquiry into the prevalence of late sequelae in spite of a certain amount of evidence (5-8) that residual damage from the disease is minimal.

The present investigation was designed as a pilot study to determine, by standard methods (9-11), whether a group of men having had scrub typhus in World War II showed, by their subsequent records of mortality, hospitalizations, disability, or present health status, evidence of sufficient residual damage from the disease to warrant a more extensive inquiry into the problem. The evidence is given below for our conclusion that the indications of significant residual damage in a group of individuals not receiving specific therapy, while they may become more clearly discernible in the future, do not suggest the need for a broader or more intensive study at present.

METHODS

SAMPLING PROCEDURES

The control sample, which had been used in another study (10), consisted of 521 men

TABLE 1. Composition of Study Sample and Reply to Questionnaire

	Number of Men
Composition of sample	
Control series (southwest Pacific combat units (10))	521
Scrub typhus series	524
Personal roster (Twentieth General Hospital)	323
Other, from Office of the Surgeon General's files*	201
Total	1,045
Questionnaire follow-up scrub typhus series	
Exclusions	50
Known dead	24†
Segregated for clinical study	25
Doubtful diagnosis	1
Questionnaire mailed	474
Undelivered	44
Replied	383
Failed to reply	47
Total	524

* In all, 471 were in the Army Office of the Surgeon General's punch-card file and 53 were not.

† One death occurred after December 31, 1955.

drawn at random from early combat units in the Southwest Pacific Theater of Operations. This group served somewhat earlier in the war in a different geographical area, but the artifacts thus introduced were thought to be minor. The scrub typhus series is largely from *Merrill's Marauders* (12) and was derived from two sources: 201 cases from the Surgeon General's file for the China-Burma-India Theater of Operations, and 323 cases from the personal rosters of patients seen by the Hospital of the University of Pennsylvania group at the Twentieth General Hospital, which was located at Margherita, Assam, India (Table 1). The cases from the private rosters were observed in 1944 and 1945, and most were subjects of a previous study describing the acute and early convalescent periods of the disease. Their original hospital records were available for the most part, and indicated that most had had either severe or grave forms of the disease as described in that communication (4).

METHODS OF STUDY

The records of the China-Burma-India scrub typhus group were studied in the following respects: (a) mortality, obtained from central files of the Veterans Administration; (b) hospital admissions following the acute illness, obtained from Veterans Administration claims folders, in Army records, and by direct mail questionnaire; (c) disability status, with cause and percentage rating obtained from Veterans Administration claims folders; (d) responses to the mail questionnaire concerning present symptoms, general health, working capacity, and changes in occupation for health reasons.

The clinical follow-up studies were carried out at the University of Pennsylvania Diagnostic Clinic in 1956 and 1957. Initially 25, and ultimately 31, men among those listed on the personal roster as severely or gravely ill were invited to par-

ticipate in these studies.* They included: complete history, with special attention to work record and morbidity in the postwar period; physical examination; ophthalmological consultation; complete neurological examination including electroencephalogram and audiogram; psychiatric consultations; and laboratory work, including complete blood count, urinalysis, erythrocyte sedimentation rate, fasting blood sugar, blood urea nitrogen, total serum cholesterol, serologic tests for syphilis, and *Proteus* OX-K agglutination. Radiograms of the chest and standard 12-lead electrocardiograms were made. Pulmonary function tests consisted of the following measurements: inspiratory capacity, expiratory reserve volume, vital capacity, residual volume, functional residual capacity, total lung capacity, alveolar gas uniformity, diffusing capacity, maximal breathing capacity, and airway resistance before and after bronchodilators.

RESULTS

INTENSIVE CLINICAL SURVEY

In general, none of the 16 subjects seen in the Diagnostic Clinic disclosed clear evidence that severe scrub typhus had left residua detectable 11 to 13 years later. Deviations from clinical norms were encountered, but they followed no discernible pattern and, with two exceptions, seemed no more frequent than one would expect in any similar group of males ranging from 31 to 51 years of age. The two exceptions, discussed more fully below, were (a) six of the 16 subjects had abnormalities of the

* If important residuals exist among some, but not all, men who survived an illness, there is a calculable risk that a small sample will actually contain none exhibiting such residuals. With random samples of 20 men, the risk that none will exhibit such a residual is 12% if the "true" proportion with residuals is one-tenth, and 1% if the "true" proportion is one-fifth. In view of such considerations, and of the costs associated with intensive clinical review of any single man, the objective was set at 20 men of whom 16 were ultimately obtained.

electroencephalogram; and (b) six were considered by the psychiatrist to have had evidence of significant psychiatric abnormality. In neither type of abnormality was any relationship to scrub typhus established. Most impressive was the fact that, in spite of the large number of abnormalities observed in these men during the acute illness, all of them during the postwar period had promptly resumed gainful occupations and, when seen, were leading normally active and useful lives. Only one of the 16 felt that his attack of scrub typhus had permanently affected his health.

HISTORY

After a period of convalescence, four had been considered to have fully recovered and were reassigned to duty in the China-Burma-India Theater of Operations; their subsequent health records were good. Seven were evacuated to hospitals in the United States for convalescence and later were returned to military duty here. Four returned to the United States as patients and remained in hospitals for varied periods until separation from service, and one was immediately separated from service on return to the United States. In response to the question, "How soon after your illness did you feel entirely well?" 11 replied that they were in their usual health within six months, and three within nine to 12 months. One complained of weakness up to two years after the attack, and one stated that he had not felt entirely well since his Army service. All of them returned to civilian employment promptly upon separation from service; only one subsequently changed his job because he found it beyond his physical capacities. All have continued to support their families through steady employment. Fourteen have exceedingly good morbidity records, and only two have had repeated illness not, however, believed to be related to scrub typhus.

PHYSICAL EXAMINATION

None of the 16 subjects presented significant abnormalities on physical examination. Minor deviations were noted, but they occurred in various body systems in an entirely haphazard fashion. In only one case was a slight elevation of blood pressure noted, 148/90 mm Hg, and in each the cardiac examination was negative. Two individuals seemed to have mild vasospasm in the lower extremities, as judged by cold, sweaty feet and pulses of reduced volume. In the more marked of these, a vasodilatation test revealed a low normal capacity for blood flow in the lower extremities and normal flow in the upper. In five individuals the permanent scar of the original eschar was found. In no instance was the spleen enlarged. Of the many extra- and intra-ocular changes in the acute phases of the disease, described by Scheie (13) and others (14-16), no residua remained. The eyes of all 16 men were examined and found to be normal.

NEUROLOGICAL EXAMINATION

In general, the interim histories of these patients were not suggestive of neurological disease. However, of three who described intolerance to heat following the acute illness, one had fainted in hot weather. The latter history suggested the distant possibility of a central loss of heat regulation as an aftermath of encephalitis accompanying the acute disease. Eleven individuals had totally negative neurological examinations. Minor abnormalities of uncertain significance were noted in five: two men had questionable Babinski's signs with no confirmatory evidence of pyramidal tract disease; in one the abdominal reflexes and knee and ankle jerks on the right were depressed in comparison with those on the left; in one a slight loss of hearing was noted in the left ear; and in the fifth the right Achilles reflex was less active than the left. In summary, it is clear that no neurological defects of

clinical significance remained in this group of men, all of whom originally had signs and symptoms suggesting acute neurological damage. In spite of the rather high incidence of positive electroencephalographic findings described below, no clinical evidence of seizures was found.

Electroencephalographic Findings: In six men the electroencephalogram was considered abnormal. The reports read as follows:

Case 1: There was a rather well-defined focus of abnormal cortical activity in the left frontal area. It was characterized by theta activity and some spiking.

Case 2: The record contained paroxysms of short runs of theta activity. This was bilaterally synchronous and most marked in the temporal areas. There was marked alpha driving over a wide range of photic driving frequency.

Case 5: There was an area of slow wave production and spiking centering about the left temporal region.

Case 11: There were two areas of abnormal slow wave production in the right and left temporal areas. There was occasional bilateral cross-modulation synchronizing this activity with voltage augmentation, but either may be seen to operate independently.

Case 14: There was a focus of abnormal slow wave activity in the left temporal region.

Case 16: This patient had short and paroxysmal runs of theta activity of moderate voltage in the frontal and temporal area bilaterally. This is not pathognomonic, but may represent an expression of subcortical aberrant activity.

PSYCHIATRIC EXAMINATION

Ten of the examinees showed no evidence of psychiatric disease. In six there was sufficient suggestion of psychopathology to warrant recommendation of further evaluation or treatment, or both.

Case 1: A tense, depressed, irritable man who complained of severe "migrainous"

headaches, searing burning pains in the middle of his chest, insomnia, and marked irritability. He stated that he was in good health and had never experienced any of the above symptoms prior to military service. His former personality was that of an outgoing, athletic individual with perfectionist trends. Since discharge he had had trouble in his relationships with many people, had divorced his wife, and had jeopardized his job by attacking another man. It is of interest to note that he had a definitely abnormal electroencephalogram with a suggested focus.

Case 6: A neat, pleasant man who showed little anxiety but who enumerated many complaints, including muscular pains in the shoulder and neck regions which at times totally incapacitated him, difficulty in breathing, a sensation of fright with palpitations before falling asleep at night, frequent heartburn, marked nervousness and irritability, a change in personality, and some concern about his memory. Apart from the muscular symptoms which came on in the military service, he felt that his other difficulties had begun, or had become much worse in the past three years. In addition to typhus, he had had both malaria and a luetic infection in military service. He expressed much guilt and concern about the latter. He consulted a physician only when his neck pains were so bad that he "needed a needle to knock him out." No evidence of abnormal cortical activity was seen in the electroencephalogram.

Case 10: A business executive who felt that he had no residuals of his typhus infection, but who had had considerable gastrointestinal dysfunction since his return to civilian life. He had been told that he had "spastic colitis" and had retreated from an excellent job opportunity to the security of a family business with resultant diminution in symptoms. His history revealed lifelong problems related to feelings of inadequacy, insecurity, and fear of competition. In spite of the fact that he could

cite no evidence of residual damage from his illness, he expressed some concern that his severe typhus infection might have permanently incapacitated him, particularly in the areas of sexual potency and mental functioning. His electroencephalogram was normal.

Case 11: A pleasant young man who expressed concern about his cardiac status. He had been quite apprehensive at the time of discharge from military service and at examination felt that his fears were justified by the 50% disability rating given him by the Veterans Administration. Although subsequently assured that his heart was normal, he has at times developed symptoms, usually under the pressure of marital or job problems. He has obtained quick relief when reassured and given "nerve medicine" by his family doctor. His electroencephalogram showed bitemporal abnormal slow wave activity.

Case 13: A somewhat anxious man who complained of severe occipital headaches occurring every three to five months and lasting about an hour. He stated that he had first experienced such headaches when he had had typhus and that they had recurred regularly ever since. Before and during military service he had experienced many minor behavior difficulties and sustained an unusual number of fractures and other accidental physical injuries. At examination he claimed that his behavior was now much better controlled but that he had temper outbursts and daydreams. The electroencephalogram was normal.

Case 14: A tense young man who complained of recurrent headaches, mood swings, and stomach pains. He stated that following his typhus infection he had been quite tense and irritable, and that his family had expressed concern about his changed personality. He felt that the symptoms described were not now bothersome except when he was upset about problems related to his job. A highly organized, serious person, he stated that he insisted on strict

discipline in himself and others. He had had convulsions as a child. His electroencephalogram showed an abnormal slow wave focus in the left temporal region.

Laboratory Findings: Occasional deviations from normal were noted in certain of the laboratory tests (Table 2). They appear to occur at random, and no consistent pattern of damage emerges. The observed abnormalities cannot, in our opinion, be convincingly related to the earlier episode of scrub typhus.

SPECIAL STUDIES

Table 3 contains the results of electrocardiograms, pulmonary function studies, radiological examinations of the chest, audiograms, and electroencephalograms. All were considered normal except for the electroencephalograms discussed above, and the audiograms, which were normal in eight but abnormal in five individuals. In these latter, the audiograms were normal over the range of sound involved in useful hearing: 256 to 2,048 cycles per second, but hearing was bilaterally decreased at the frequency of 4,096 by an average of 40 decibels. At frequency 8,192 the impairment was less marked, the average loss in decibels being only 28. This is the usual pattern of nerve type of deafness, leaving the individual with serviceable hearing but with a deficit in perception of high tones which is maximal at a frequency of 4,096 cycles per minute.

RECORD STUDY

Mortality: Twenty-three deaths occurred between January 1, 1946, and January 1, 1956, in the scrub typhus group of 524 men. However, only 11 were due to disease, the remaining 12 being due to accidents, 6; battle casualties, 3; suicide, 2; and homicide, 1. The 20 deaths not attributable to combat are significantly ($P < .03$) in excess

TABLE 2. Laboratory Results in 16 Men Examined in the Diagnostic Clinic

Subject	Hemoglobin (g/100 ml)	Blood Count (white blood cells per cubic mm)	Differential	Urinalysis	Sedimentation rate (mm/hr)	Fasting Blood		Cholesterol	Serological Test for Syphilis	<i>Proteus</i> OX-K Agglutination
						Blood Sugar	Blood Urea Nitrogen (mg./100 ml)			
1	16.0	11,100	Normal	Negative	10	77	16	212	Nonreactive	Negative
2	15.9	6,200	Normal	Negative	4	92	15	231	Nonreactive	Negative
3	15.7	7,600	Normal	Negative	4	91	12	164	Nonreactive	Negative
4	17.2	8,500	Normal	Negative	14	73	19	288	Nonreactive	Negative
5	17.8	4,300	Normal	Negative	12	100	17	229	—	—
6	17.5	13,800	Normal	Negative	21	83	23	231	Nonreactive	Negative
7	17.1	5,800	Normal	Negative	7	90	11	246	Nonreactive	Negative
8	17.5	7,400	Normal	Negative	7	72	16	294	Nonreactive	Negative
9	16.5	6,000	4% eosinophils	Negative	13	67	14	258	Nonreactive	—
10	16.2	4,000	Normal	Negative	7	75	11	220	Nonreactive	—
11	16.5	6,200	Normal	Negative	9	75	10	178	Nonreactive	—
12	15.3	5,100	4% eosinophils	Negative	18	73	11	341	—	Negative
13	16.1	8,900	Normal	Negative	18	80	13	—	Nonreactive	Negative
14	16.2	4,000	4% eosinophils	Negative	5	94	9	191	Nonreactive	Negative
15	16.5	5,300	3% eosinophils	Negative	12	72	16	233	Nonreactive	Negative
16	16.4	10,700	Normal	Negative	10	86	12	250	Nonreactive	—

TABLE 3. Results of Special Studies on 16 Men Examined in Diagnostic Clinic

Subject	Electro-cardiogram	Chest X-ray	Pulmonary Function	Audiogram	Electro-encephalogram
1	Normal	Negative	—	Normal	Abnormal
2	Bradycardia	Negative	—	—	Abnormal
3	Normal	Slight cardiac enlargement	Normal	Normal	Normal
4	Normal	Negative	Normal	Normal	Normal
5	Normal	Negative	Normal	Abnormal	Abnormal
6	Normal	Negative	—	Normal	Normal
7	Normal	Negative	Low diffusing capacity (carbon monoxide)	Normal	Normal
8	Normal	Negative	Normal	—	Normal
9	Normal	Negative	Normal	Abnormal	Normal
10	Normal	Negative	—	Normal	Normal
11	Normal	Negative	—	Abnormal	Abnormal
12	Normal	Negative	Normal	—	Normal
13	Ventricular premature contractions	Negative	Normal	Normal	Normal
14	Normal	Negative	Normal	Normal	Abnormal
15	Normal	Negative	Normal	Abnormal	Normal
16	Normal	Negative	—	Abnormal	Abnormal

of the 12.3 expected* for American white males of equivalent age. The difference is largely attributable to deaths from accidents, suicide, and homicide; the 11 deaths from natural causes do not differ significantly ($P > .10$) from the 7.2 expected.* The natural causes of death were: cardiovascular disease, 3; hepatic disease, 3; malignant disease, 2; lobar pneumonia, 1; pulmonary tuberculosis, 1; and glomerulonephritis, 1.

In Table 4, when mortality from causes not attributable to combat was related to the severity of the original disease, we found relatively fewer deaths among those who had been severely or gravely ill from scrub typhus.

* Calculated from life tables for white males, National Office of Vital Statistics, then distributed as to cause according to pattern for men of stated age in each calendar year of exposure.

Hospital Admissions: A comparison was made of the scrub typhus and control groups with respect to admissions to Army and Veterans Administration hospitals during the period 1946 through 1951. The comparison revealed that the average rate of admission during that period for both groups was 62 per 1,000 men per year. For the scrub typhus group the rate was 71 and

TABLE 4. Mortality versus Severity of Illness

Type of Case	Number of Men	Number of Deaths	
		Observed	Expected
Severe and grave	140	4	3.3
Other, including unknown	384	16	9.0
Total	524	20	12.3

for the controls 53. Although these rates differ quite significantly in the statistical sense, half of the discrepancy derives from the rates for infectious and parasitic disease; otherwise there is no particular pattern to the variation.

From observing the acute disease one might have expected severe residual damage, especially in the cardiovascular, cerebral, pulmonary, or renal systems. A study of the causes for admission in the control versus the scrub typhus groups does not suggest that such was the case. For each of these rubrics, and for all four combined, the differences lay well within the range of chance and suggested no continuing influence of scrub typhus. Similarly negative results were obtained when hospital admissions were grouped by cause and severity of the original disease. No indication was found that disease of any particular body system characterized the subsequent admissions of those who had originally been severely or gravely ill. Also, the frequency of subsequent admissions was unrelated to severity of the original disease. The admission rates appear in Table 5.

Disability Status in the Veterans Administration: In the combined scrub typhus and control groups 1,027 men were found with technically adequate information concerning Veterans Administration compensation for disabilities connected with the service. Information in Table 6 on controls was obtained in 1952, while that on the scrub typhus group was obtained in 1956.

An internal comparison in Table 7 of the scrub typhus group classified by severity of illness brought out a significant difference.

Responses to the Questionnaire: Current

TABLE 5. Hospital Admissions Grouped by Severity of the Original Illness

Total (524 men)	71
Severely or gravely ill (140 men)	63
Mixed (201 men)	78
Mildly or moderately ill (183 men)	70

TABLE 6. Veterans Administration Disability Rating of 10% or More in the Combined Scrub Typhus and Control Groups

Group	Disability Rating of 10% or More
Total (1,027 men)	26%
Controls (516 men)	29%
Scrub typhus (511 men)	23%

TABLE 7. Scrub Typhus Group Classified by Severity of Illness

Group	Disability Rating of 10% or More
Severe and grave (133 men)	29%
Mixed (198 men)	26%
Mild or moderate (180 men)	16%

complaints were reported by 243, or 63% of the 383 veterans who responded to the questionnaire (Table 1). Since comparable data on controls were not available, we sought a relationship between severity of original illness and both frequency and pattern of later complaints, but found none. In the statements of 24% of the respondents, no relation between present complaints and the previous scrub typhus was asserted. A relationship in whole or in part was believed to exist by 39% of the group. When those with symptoms were further analyzed, 76% whose scrub typhus had been severe or grave attributed their present ills to the disease, whereas only 50% with moderate or mild illness believed that any association existed. Approximately one-third of the respondents felt that their present health limited their ability to work and one-quarter had changed occupations for reasons of health.

DISCUSSION

CLINICAL STUDY

The clinical study of the 16 individuals has an advantage which offsets the obvious disadvantage of their small number; namely, the fact that our clinical records

of the original illness indicate that most of them had had scrub typhus in a very severe form. During the illness they gave evidence of profound damage to the cardiovascular, respiratory, and central nervous systems. The lack of evidence of late complications in our patients is consistent with the results of certain follow-up studies made a few months after recovery. Berry, Johnson, and Warshauer (5) and Levine (6) found little or no evidence of cardiovascular abnormality in patients studied one to two and one-half months after recovery from scrub typhus. On the contrary, Sokolow and Garland (7) found decrease in duration of breath-holding, tachycardia on standing and exercise, minor electrocardiographic changes, and "occasional" enlargement of the heart in a group of 35 patients studied a few months after the disease.

The interpretation of the psychiatric studies in our group is difficult. All six men who demonstrated significant psychopathology at follow-up seemed to have factors in their past history predisposing them to subsequent psychiatric difficulties. Many gave histories of appreciable deprivations in their early lives. It was impossible, on the basis of this examination, to evaluate the role which typhus infection might have played in precipitating their present symptoms. The histories suggested some temporal relationship in all, although three men believed that their symptoms were aggravated by problems in their current life situations. However, in one instance (Case 1), the first appearance of difficulties following scrub typhus justified the suspicion that his psychopathological behavior may have resulted from the disease. If it is obviously impossible to establish this relationship with certainty, it is equally impossible to deny it. In a study of 180 Australian soldiers who developed scrub typhus in New Guinea, Noad and Haymaker (8) recorded only three who, eight years subsequently, had clear-cut symptoms of psychiatric disorder, although one-third of the original

group had had, at one time following the illness, symptoms interpreted as indicative of neurocirculatory asthenia, anxiety states, and neurasthenia.

The finding of six non-specifically abnormal electroencephalograms in 16 examinations is far above the normal expectation for an unselected population sample as seen in this clinic. The interpretation of the observation is difficult. Whether or not the changes represent sequelae of encephalitis, no clinical signs, convulsive or otherwise, are correlated with them. In this connection it is of interest to review the findings of Case 2. The features of his original illness are described in detail in a previous study (4) in which he may be identified as Case 95. Of all subjects in the present study he was the most gravely ill and had the greatest evidence of central nervous system damage. For example, during the third week of illness rigidity of his neck developed and Cheyne-Stokes respiration occurred. The following week he had convolution, after which he was comatose for 12 hours. On regaining consciousness he was mentally confused, had jerking movements of his extremities, and stuttered. He remained apprehensive, querulous, and tremulous for some time thereafter. In our present review, however, he had negative neurological and psychiatric examinations, including extensive psychological tests, although his electroencephalogram contained abnormalities.

Temporary deafness was a frequent clinical feature of acute scrub typhus. Noad et al. (8) recorded residual disability in hearing in 5% of their 180 patients. Of our 16 patients, none had loss of serviceable hearing, although five had some acoustic nerve damage, evidenced by a decrease in auditory acuity for very high sounds. This type of damage, however, cannot be ascribed with certainty to the previous scrub typhus, as it has frequently been observed in soldiers who have been exposed to the percussive effects of gunfire.

RECORD STUDY

The evidence of morbidity derived from a study of hospital admissions, disability ratings, and questionnaire responses is obviously of indirect nature and is open to various interpretations. The rate of admission to Army and Veterans Administration hospitals during the period 1946 through 1951 was definitely higher for the scrub typhus group than for our control group. This cannot be dismissed as insignificant, nor can it be regarded as positive evidence of residual damage from scrub typhus. The frequency of admission was not higher in those men who had had very severe scrub typhus; furthermore, admissions were relatively few for diseases of those organ systems known to be most severely damaged in the acute stages of the untreated disease. The more frequent hospital admissions among those with previous scrub typhus are therefore of doubtful meaning and may derive from the different experiences in the two theaters of war or from differences present prior to their service in these areas.

The study and control groups did not differ in regard to Veterans Administration disability rating, but severity of the original disease was directly related to disability rating. However, compensation for ills contracted in the service is so tied to elements in the history that the observed differences may reflect the attitudes and information of those who rated the disability rather than the health of the veterans at the time the ratings were made.

The responses to the questionnaire provide the least useful evidence since they may reflect the well-known tendency of some veterans to attribute as many ills as possible to Army service, in order to establish or strengthen claims for disability compensation. The 16 men in the clinical study, admittedly a small sample, who were examined personally in a civilian setting, did not attribute their present symptoms to the previous scrub typhus with the frequency

observed in the respondents to the questionnaire, although they were known to have had a severe form of the disease.

SUMMARY AND CONCLUSIONS

A combined clinical and statistical study has been made on a representative sample of veterans who survived scrub typhus in the China-Burma-India Theater of Operations in World War II. The clinical studies were made on 16 men formerly in our care at the Twentieth General Hospital who had had severe or grave manifestations of the original illness. None had received antibiotic therapy at that time. Neither their subsequent histories nor detailed examinations and laboratory observations at follow-up gave any clear indication that significant permanent structural or functional damage had resulted from scrub typhus. However, in three respects abnormalities were encountered with unexpected frequency. First, evidence of psychopathology was judged to be present in six individuals. In no instance could it be ascribed with certainty to the scrub typhus, and in several it had clearly antedated Army service. In one instance, however, the temporal relationship between scrub typhus and subsequent psychopathological behavior seems a distinct possibility. Second, electroencephalographic abnormalities were noted in six individuals. They were not specific in nature and were unassociated with positive neurological findings. Of the six individuals with psychopathology, three had abnormal electroencephalograms and three did not. It is not possible to state with certainty whether these abnormalities are attributable to scrub typhus. Finally, five individuals had evidence of slight acoustic nerve damage, the cause of which was uncertain.

In the statistical observations a sample of 524 veterans who had had scrub typhus during World War II were studied through 1955 as to morbidity and mortality. Hospital admissions, Veterans Administration

disability ratings, and responses to a questionnaire concerning present and past health status provided the evidence. The group under study did not differ from the controls in respect to Veterans Administration disability rating. They had a higher rate of hospital admissions but these were for miscellaneous causes not thought to be related to scrub typhus, and the rate was unrelated to the severity of the original disease. Mortality in the scrub typhus group was significantly in excess of civilian expectation for all causes (20 observed versus 12.3 expected), but not so for natural causes only (11 versus 7.2). Responses to the questionnaire indicated current complaints in 63% of respondents, of whom two-thirds attributed the symptoms to the previous disease. This, however, was not regarded as clear evidence of residual damage from the disease. On the basis of all clinical and statistical evidence the conclusion is drawn that the evidence of residual damage is too slight to make it likely that a more elaborate clinical study would alter the conclusions drawn here.

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The authors are indebted to the Medical Statistics Division, Office of the Surgeon General, for having made this file available for study.

SUMMARIO IN INTERLINGUA

Un combinante studio clinic e statistic ha esiste effectuate in un selection representative de veteranos qui superviveva a febre fluvial japonese contrahite in le theatro de operationes de China-Burma-India durante le secunde guerra mundial. Le studios clinic esseva executeate in 16 homines qui habeva habite sever o grave manifestationes del morbo original. Nulle habeva recipite un therapia antibiotic a ille tempore. Ni le historias catamnestic del subjectos ni le detaliate examenes e observationes laboratorial al tempore del studios de controllo subsequente produceva ulle nette indication que formas significative de permanente alterationes structural o functional habeva resultate del febre fluvial japonese. Tamen, in tres respectos anormalitates esseva incontrate con non ex-

pectate frequentias: Evidentia de psychopathologia (in sex individuos); deviationes electroencephalographic (in sex individuos); e indicaciones de un leve grado de affection de nervo acustic (in cinque individuos). Il non es possibile asserer con certitude que iste anormalitates es attribuibile al febre fluvial japonese.

In le parte statistic del investigation, un selection de 524 veteranos, qui habeva habite febre fluvial japonese durante le secunde guerra mundial, esseva studiate usque al fin de 1955 con respecto al factores de morbiditate e mortalitate. Le statistica del hospitalisations e del classation de invaliditate del Administration de Veteranos indica que le gruppo sub investigation non differeva significativamente ab le norma. Le responsas a un questionario concernente le presente e passate stato de sanitate non produceva ulle nette indication de un connexion inter le presente symptomas e le previe morbo. Le datos del questionario non permitteva asserer le existentia de damno residue.

Super le base de omne le datos clinic e statistic, le conclusion es formulate que in le population studiate febre fluvial japonese non ha resultate in significative sequellas tardive.

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Familial Incidence of Diabetes in Hyperthyroidism

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HYPERTHYROIDISM AND DIABETES MELLITUS have certain similarities. Not only are the symptoms of the two conditions (fatigue, anxiety, and weight loss) comparable; hyperthyroid patients are more prone than normal individuals to develop diabetes, and diabetics are more apt to become hyperthyroid. Indeed, several observers have postulated that the two disorders, whose etiologies remain obscure, may be peripheral manifestations of a common central metabolic disorder (1, 2). Since diabetes is known to be an inherited disease, albeit a condition that develops late in life, and since there is a strong familial pattern to hyperthyroidism, it seemed reasonable to investigate the inheritance of diabetes in hyperthyroidism and to ascertain the possible effect that such family history might have on the clinical manifestations of the thyroid condition.

MATERIALS AND METHODS

We reviewed the charts of 335 patients who were discharged from the Grace-New Haven Community Hospital between 1953 and 1960 with the diagnosis of hyperthyroidism with or without goiter. An individual was classified as having hyperthyroidism if he had symptoms of the disease and a basal metabolism rate, radioactive iodine uptake, or blood iodine level compatible with the diagnosis. In certain rare instances if the clinical picture was classical, with weight loss, tremor, heat intoler-

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ance, and goiter, but laboratory confirmation was lacking, the patient was also accepted in the study group. According to these criteria 292 had unequivocal manifestations of the disease. The charts of 187 of these patients either specifically mentioned diabetes or the histories catalogued the various family members, so that while diabetes was not specifically mentioned it was felt that it could be excluded.

A control group of 187 patients was chosen at random with the same criteria as indicated above from the charts of 285 patients who were admitted to the Grace-New Haven Hospital and compared to the hyperthyroid group. The age distribution of 187 hyperthyroids and 187 controls is shown in Table 1. Each group contained 35 males. The major diagnoses of the controls are seen in Table 2. The per cent of charts in the control group which had adequate information on diabetes was similar to that of the hyperthyroid group (Table 3).

RESULTS

Thirteen of the 187 hyperthyroid patients had clinical diabetes mellitus. Sixty-seven (36%) of the patients with hyperthyroidism had a family history of diabetes mellitus compared with 42 (22.5%) of the controls. By the chi square method of Fisher (3) it is seen that such results would occur by chance less than once in a hundred times. It is concluded that there is a greater incidence of diabetes in the family histories of hyperthyroid patients than in controls.

There is the same percentage of males and females in both the positive and negative family history groups (Table 4). These

TABLE 1. Comparison by Age of Hyperthyroid Patients and Controls

	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
187 Hyperthyroid	0	5	32	39	31	39	18	17
187 Controls	1	6	30	39	31	39	18	17

figures, which show a female sex predominance of 4:1, agree with the sex ratio reported by Means but are somewhat at variance with the ratio of 9:1 reported in the European literature (4).

There is no significant difference in the age of onset of hyperthyroidism in those patients with positive family histories and in those with negative family histories for diabetes, although hyperthyroidism tended to develop a little earlier in the diabetes-positive pedigree group as compared to the diabetes-negative series.

Table 5 shows blood iodine levels before treatment (butanol extractable iodine or protein bound iodine) for 51 patients with

TABLE 2. Principal Diagnoses of 187 Control Patients

Diabetes	13
Gastrointestinal disease	28
Gynecological disease	14
Cardiovascular disease	25
Neoplasia	21
Elective surgery	15
Infectious disease	37
Functional illness	5
Miscellaneous	29
Total	187

TABLE 3. Comparison of Hyperthyroid Patients and Controls: Chart Information Relating to Family History of Diabetes

	No. with Information	Number Read	Per Cent
Hyperthyroid	186	292	64
Control	187	285	66

TABLE 4. Comparison of Hyperthyroid Patients with Positive and Negative Family Histories of Diabetes with Respect to Sex

	Male	Female
67 hyperthyroids with positive family history for diabetes	13 19.5%	54 80.5%
120 hyperthyroids with negative family history	23 19.2%	97 80.8%

diabetes-positive family histories and for 91 with negative family histories. Normal range for both is 3.2 to 6.2 μg per 100 ml. Note that 80% of the positive pedigree group had blood iodine values over 9, while 57% in the negative group had such values. Such results would occur by chance less than one time in a hundred. At higher levels of blood iodine the difference between the two groups is less marked but the general trend is for the diabetes-positive pedigree to have the higher blood iodine level. For example, 41% of the diabetes-positive group have values over 12 as compared to 25% of the diabetes-negative group. The possibility that this could occur by chance is less than one in twenty.

Radioactive iodine uptake is not as well correlated with clinical severity as the butanol extractable iodine or the protein bound iodine. However, patients with family histories of diabetes had a higher percentage of greatly elevated radioactive iodine uptake before treatment than did patients without such histories (Table 6).

TABLE 5. Comparison of Hyperthyroid Patients with Positive or Negative Family Histories of Diabetes: Blood Iodine Levels

	6-6.9	7-7.9	8-8.9	9-9.9	10-10.9	11-11.9	12-12.9	13-13.9	14-14.9	15-15.9	16-23
51 hyperthyroids with positive family history	2 4%	3 6%	5 10%	7 13.5%	8 15.5%	5 10%	7 13.5%	4 8%	2 4%	1 2%	7 13.5%
91 hyperthyroids without family history of diabetes	7 7.7%	19 21%	13 14.3%	14 15.5%	13 14.3%	13 3.2%	7 7.7%	3 3.2%	3 5.5%	1 1.2%	6 6.4%

TABLE 6. Comparison of Hyperthyroid Patients with Positive or Negative Family Histories of Diabetes: Per Cent of Radioactive Iodine Uptake in 24 Hours

	Less Than 50	50-59	60-69	70-79	80-89	90-99	Greater Than 100
26 hyperthyroids with positive family history	0 0%	0 0%	6 23%	4 15.5%	6 23%	4 15.5%	6 23%
40 hyperthyroids with negative family history	1 2.5%	4 10%	9 22.5%	10 25%	10 25%	2 5%	4 10%

DISCUSSION

It has been generally thought that the causal relationship between diabetes and hyperthyroidism was that the latter was a predisposing factor, or that it revealed the former. Amelioration of the diabetes through lessening the need for insulin by thyroidectomy or by antithyroid medication substantiated this view (3, 5-7). It was also reported that a hyperthyroid was three times more likely to develop diabetes than were patients in the general population (8, 9, 10). Diabetes so uncovered was considered to be more resistant to insulin and more prone to ketosis. The rarity of the association between hypothyroidism and diabetes enhanced this causal theory (11).

The concept that diabetes predisposes patients to hyperthyroidism has not received as much attention. However, diabetes precedes hyperthyroidism clinically in the ma-

jority of patients with both diseases. Joslin, Root, White, and Marble report that in 67% of 86 patients the diabetes developed first (12). Ralli, Street, and Pell (13) show that 12% of their diabetics developed hyperthyroidism, while Bowen and Lenzner noted that diabetes appeared first in the majority of their cases (7).

The incidence of diabetes in the family histories of hyperthyroid patients has also received little attention. Bartels reviewed the material in Denmark, where hyperthyroidism is a common disease, and concluded that a family history of diabetes is no more common in this group than in the general population (14). However, Joslin reports that 52% of his patients with hyperthyroidism and diabetes have family histories (parents and siblings) of diabetes as compared to 6.7% of diabetics generally (12). In a small series Bowen and Lenzner showed that 55% of their diabetic patients

with hyperthyroidism had such family histories (7).

The mechanism by which diabetes predisposes patients to hyperthyroidism and the reason why such hyperthyroidism should be associated with higher blood iodine levels can only be speculated on.

SUMMARY

1. There is a significantly increased incidence of diabetes in the pedigrees of patients with hyperthyroidism compared to a control series which is matched for age and sex.

2. The hyperthyroid patients with positive family histories for diabetes are somewhat younger and have more severe diabetes, as measured by clinical and laboratory findings, than those with diabetes-negative family histories.

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SUMMARIO IN INTERLINGUA

Il existe un significativemente augmentate incidentia de diabete in le consanguineos de pacientes con hyperthyroidismo in comparation con un serie de controlo appareato in etate e sexo. Le pacientes hyperthyroide con historias familial positive pro diabete es un pauc plus juvene e ha diabete plus sever (secundo le constataciones clinic e laboratorial) que illes con historias familial negative pro diabete.

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The Clinical Syndrome of Amebic Abscess of the Left Lobe of the Liver

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ALTHOUGH EXTENSIVE LITERATURE EXISTS ON amebic abscesses of the right lobe of the liver, comparatively little attention so far has been given to amebic necroses of the left lobe. The reason for this paucity of clinical observations is illustrated by Munk's remark (1): ". . . the x ray symptomatology of amoebic hepatitis is limited in the main to indirect signs on the right half of the diaphragm and the right lower lung field." (Amoebic hepatitis affecting the left liver lobe exclusively is not included in this paper, as no definite cases have been encountered.)

Single case reports are available from North Africa and from India (2, 3). Lamont and Pooler (4), and Paul (5) have recently given attention to problems connected with left lobe abscesses in their papers on large series of amebic abscesses of the liver.

We have found amebic abscesses of the left lobe of the liver, though comparatively rare, to be a well defined clinical entity, distinct from right lobe abscesses. The knowledge of this syndrome facilitates an early diagnosis leading to timely and efficient treatment in most cases, while a high mortality ensues in protracted cases, and after complications have developed.

In this paper an attempt will be made to differentiate the two types of liver ab-

scusses as well as to consider the differentiation of left lobe abscesses from diseases affecting neighboring structures of the left lobe outside the liver.

The study is based on clinical, radiological, and laboratory observations in eight patients. Five were admitted to the Asaf Harofe Government Hospital, Zrifin (one later died in the Beilinson Hospital), and three to the Donolo Government Hospital in Jaffa.

In four cases the diagnosis became evident at operation, in three it was established only at post-mortem examination, and one patient recovered with conservative treatment.

ANATOMICAL CONSIDERATIONS

The clinical course of left lobe abscesses as distinct from those of the right liver lobe, necessitates the anatomical delineation of the left lobe and its surroundings.

The right lobe, approximately twice the size of the left, occupies the whole of the right subdiaphragmatic space. Its broad fixation by ligaments, particularly in the region of the caval vein, allows just for limited mobility of the right lobe. On the other hand, only about half of the left diaphragmatic leaf is in contact with the left lobe which is attached to the posterior aspect of this part of the diaphragm by the comparatively delicate triangular ligament (Figure 1) (6).

Abscesses of the right lobe show a tendency to develop in its upper part (7, 8) and to encroach on the diaphragm, as there is less resistance in that direction than against

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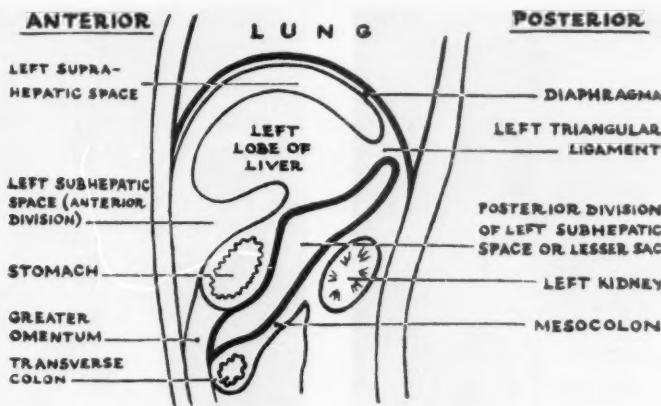


FIGURE 1. Left parasagittal section through abdominal viscera.
Modified after Callander (10).

the dense bulk of the liver (6, 9). The left lobe is much thinner, particularly in its vertical diameter, and an abscess growing in this area is apt to extend upward, but more often downward, as the abdominal cavity offers less resistance. Here the adjacent structures are the stomach, the lesser sac, and the large intestine, while on top of the left lobe and above the left suprahepatic space the diaphragm is lined laterally by the pleural cavity, and more medially by the pericardial sac.

CASE REPORTS

CASE I

A 51-year-old woman emigrated six years previously from Tripolitania. There was no contributory past history. High pyrexia, night sweats, anorexia, and loss of weight occurred two months prior to admission, with pain in the left hypochondrium, not connected with meals. Bowel movements were normal. When her condition deteriorated, the patient was hospitalized.

Physical examination showed a pale and cachectic woman, crying with abdominal pain. The temperature was 100.8 F, and the pulse rate was 100/minute, regular. Blood pressure was 110/80 mm Hg. The abdomen was soft and the liver not palpable in the right hypochondrium. Under the left costal margin a hard, tender, and smooth tumor of grapefruit size was evident.

Laboratory Data: The blood sedimentation rate was increased to 110 mm in the first hour (Westergren). The Weltmann coagulation band was shortened to 1. Hemoglobin, 9.5 g/100 ml; erythrocytes, 2,900,000/mm³; leukocytes, 6,800/mm³, with a shift to the left. Blood cultures remained sterile. A Casoni skin test and Weinberg's complement fixation test were negative. Apart from a slightly increased thymol turbidity (7 units), liver function tests were normal. X-ray examination of the heart showed an enlarged left ventricle, while the lungs and diaphragm were normal. A straight abdominal film revealed a mass unconnected with the spleen in the left hypochondrium. On barium meal there was a spherical mass exerting pressure on the greater curvature of the stomach from left to right (Figure 2), and also from front to back (Figure 3). Stools were not examined for parasites.

Hospital Course: Laparotomy, performed on suspicion of an abdominal tumor, revealed a greatly enlarged left liver lobe adherent to the anterior abdominal wall. When the adhesions were separated, thick, malodorous, greyish-yellow pus spurted out. This pus was sterile and did not contain amebae. Postoperatively tetracycline, chloroquine, emetine, and diiodohydroxyquin were given. The temperature dropped to normal and the blood sedimentation rate to 40 mm in the first hour. The patient was discharged in a satisfactory condition 21 days after operation.

Comment: The patient evidenced a syndrome with fever, severe abdominal pain, and a tumor in the left upper quadrant of the abdomen.

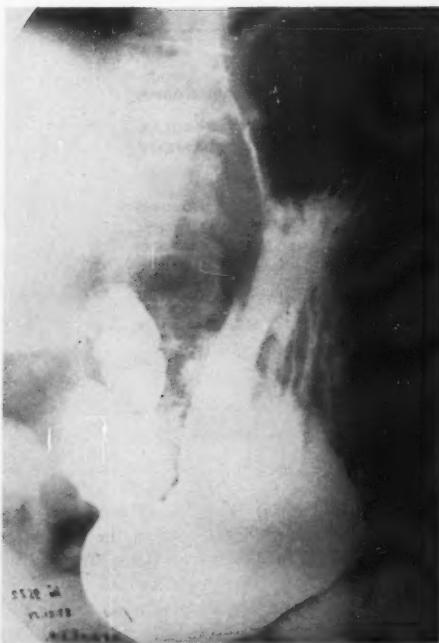


FIGURE 2. Anteroposterior film of barium meal with signs of pressure on upper part of greater curve of stomach (Case 1).



FIGURE 3. Lateral film of barium meal showing backward displacement of stomach (Case 4).

There was a good clinical response to antiamebic treatment after drainage of an abscess of the left liver lobe. Several points are stressed:

1. The patient was a female. Women are rarely affected by amebic liver complications, such as abscesses.
2. There was no previous history of bowel disturbances, not an unusual feature in extraintestinal amebiasis.
3. Absence of leukocytosis. Lamont et al. (4) found a normal leukocyte count in 18% of 230 cases. Manson-Bahr (11) found the same in 12% of 45 patients with amebic abscess.
4. The barium meal was indicative of a mass originating from the left lateral tip of the liver, pressing against the stomach.
5. The pus, though of a color uncharacteristic for amebic abscess, was sterile without prior antibiotic treatment.
6. The favorable clinical response to antiamebic therapy following surgical intervention supported the assumption of an amebic origin of the abscess.

CASE 2

A 66-year-old male emigrated 41 years earlier from the Yemen. There was no contributory past history of diarrhea. Rigors and temperature up to 102.2 F, chest pain on breathing, and severe cough appeared suddenly ten days prior to admission. Five days later jaundice was noticed which lasted only for several days.

On physical examination the patient was found in a satisfactory general and nutritional state, though he had somewhat cyanosed lips and mild dyspnea. There was a temperature of 101.1 F, but no further abnormality was detected on admission.

Laboratory Data: The blood sedimentation rate was 20 mm in the first hour (Westergren). Leukocytes, 9,500/mm³, with a normal differential count. Thick blood smears were negative for blood parasites. The blood bilirubin reached 0.8 mg/100 ml, the upper limit of normal. No bilirubin, but increased urobilinogen was found in the urine. Stool examinations were negative for *Entameba histolytica*. A chest radiography showed an enlarged left ventricle of the heart and enlarged hilar shadows.

Clinical Course: On suspicion of a pneumonic process penicillin was given. The temperature became subfebrile, the patient felt better, and he insisted on being discharged from the hospital. Soon after returning home, he began to complain of retrosternal pain and dyspnea. He was admitted to the Beilinson Hospital with the tentative diagnosis of "myocardial infarction." On examination pyrexia was found, and dullness and crepitations over both lung bases. In the right hypochondrium a mass suggestive of a congested gall bladder or an enlarged liver was palpated. Five days later the patient complained of severe, generalized abdominal pain. A straight abdominal X ray showed considerable distention of the small intestine and numerous fluid levels. On chest radiography a homogeneous density involving the whole lower lung field was found. Some improvement followed symptomatic treatment, and the density in the lung disappeared. The temperature again became subfebrile. Another stool examination revealed cysts of *Entameba histolytica*. During the fourth week after admission an ill-defined resistance was palpated in the right hypochondrium, and jaundice was noticed again. Blood bilirubin now rose to 9 mg/100 ml. After initial treatment with streptomycin, emetine was added, but the patient died several days later with signs of an acute abdomen.

Post-mortem Examination: This examination revealed purulent peritonitis, enlargement of the right lobe of the liver, and complete destruction of the left lobe. In its place a large cyst was seen, adherent to the left diaphragm, and with an opening into the lesser sac. The cyst was filled with a brownish-yellow, pulp-like mass. The surroundings of the portal vein were edematous. The bile ducts were patent. Hydrops of the gall bladder was present.

Comment: A protean syndrome presenting itself at first as pneumonia, later as stenocardia, and, finally, as cholecystitis with hydrops of the gall bladder. The course was complicated by acute abdominal signs due to perforation of an abscess of the left liver lobe (found only after death) into the lesser sac and the free peritoneal cavity, with ileus as the leading sign. The jaundice and hydrops of the gall bladder during the final stages are explained by the pressure exerted on the common bile duct following an initial perforation of the abscess into the lesser sac, and by edematous tissue on the porta hepatitis, or both. Initially, the blood sedimentation rate was raised very little, and the white cell count was normal. Follow-up examinations were not available.

CASE 3

A 46-year-old male who emigrated seven years previously from Poland was admitted for fever and retrosternal pain. Six months earlier the patient was found to be generally healthy. Five months prior to admission he began to complain of pain in his left chest and shoulder and irregular fever then occurred. For two weeks prior to admission he complained of a dry cough. There was no past history of diarrhea.

On physical examination the man was in satisfactory general and nutritional state, with a temperature of 100 F and tachycardia of 140/min. The blood pressure was 140/90 mm Hg. Heart, lungs, and abdomen were without any abnormality.

Laboratory Data: The blood sedimentation rate was increased to 62 mm in the first hour (Westergren), and Weltmann's coagulation band was shortened to 2. Hemoglobin, 11 g/100 ml; erythrocytes, 3,600,000/mm³; leukocytes, 11,500/mm³, with neutrophilia. Liver function tests showed only a positive cadmium sulfate reaction. Blood cultures remained sterile and thick blood smears were negative for blood parasites. Urine urobilinogen was increased. On X-ray examination of the chest enlargement of the left ventricle of the heart, a prominent pulmonary artery, and adhesions in the left costophrenic angle were seen.

Hospital Course: During the first days after admission the temperature rose to 102.2 F. On the fourth day the patient complained of retrosternal pressure which was accompanied by shock. An electrocardiogram showed changes indicative of pericarditis. Leukocytes were increased to 23,600/mm³. The blood sedimentation rate rose to 114 mm in the first hour. An additional X ray of the chest showed a grossly enlarged heart silhouette and considerable pulmonary congestion. Two days later dullness and crepitations were found over the left lung base. On needle exploration 600 ml sterile, chocolate-colored pus were removed from the pericardial sac. No amebae were found, and examination for tubercle bacilli was negative. Additional evacuations became necessary. The color of the pus aroused suspicion of an amebic infection, and emetine was given. During the seventh week the patient suddenly lost consciousness and developed convulsions and right hemiplegia. Several days later he died. The only available details of the post-mortem examination were subphrenic abscess with perforation into the pericardium, purulent peri-



FIGURE 4. Anteroposterior film of barium meal showing displacement of stomach to the left (Case 4).

carditis, atelectasis of the left lung, metastatic brain abscesses, cerebral edema.

Comment: An illness of five months' duration with high pyrexia and pain in the left chest radiating to the left shoulder was noted. The blood sedimentation rate and leukocytes were increased and the Weltmann coagulation band was shortened. The syndrome was complicated by purulent pericarditis. The chocolate-colored pus contained sterile necrotic material. On post-mortem examination a subphrenic abscess was found with perforation into the pericardium. A primary subphrenic abscess containing chocolate-colored pus, in the absence of any other illness, past or present, particularly in an area where amebiasis is endemic, is highly suggestive of an amebic origin. This reasoning is supported by similar observations in the literature (4, 7, 12-15). De Bakey and Ochsner (7) point out that necrotic, chocolate-colored material without red blood cells, as also found in this case, can only originate in the liver.

CASE 4

A 60-year-old Bedouin Arab was admitted because of an acute abdomen, the complication of a suspected tumor. The patient claimed no illness until 40 days prior to admission, when diarrhea with blood, epigastric pain, weakness, nausea, vomiting, and cough were noticed. In the week prior to hospital admission his condition deteriorated.

On physical examination the apyrexial patient was found to be in a poor general and nutritional state. The pulse was 80/minute and the blood pressure 100/60 mm Hg. Considerable epigastric tenderness and muscular resistance were evident, and an ill-defined tumor was felt. On account of the muscular resistance it was not possible then to palpate liver or spleen. No other abnormal findings were detected.

Laboratory Data: The blood sedimentation rate was increased to 122 mm in the first hour (Westergren), and Weltmann's coagulation band was shortened to 1. Hemoglobin, 9.5 g/100 ml; erythrocytes, 3,100,000/mm³; leukocytes, 11,500/mm³, with a shift to the left. Liver function tests showed an increased thymol turbidity up to 10 units and thymol flocculation was 3 plus. Serum bilirubin was within normal limits. Serum globulins were increased. Thick blood smears were negative for blood parasites and blood cultures remained sterile. The urine was without abnormal findings. No amebae were found in the feces. The Casoni test was negative, while Weinberg's complement fixation test was weakly positive. X-ray studies of the chest showed a high standing left diaphragm with limited movements, some fluid in the left costophrenic angle, and flat atelectases in the left lower lung. A barium meal revealed signs of pressure on the stomach from right to left and from front to back (Figure 3). Consequently, the stomach was sickle-shaped (Figure 4). A barium enema was normal.

Hospital Course: Initially antibiotics were given, and fluid administered parenterally. During the following days there was less muscular resistance and it became possible to palpate a grapefruit-sized, cystic, and tender mass to the left of the epigastrium, connected with the liver. The entire left hypochondrium was occupied by the extremely tender left liver lobe which, on inspiration, descended together with the cystic mass up to 10 cm below the left costal margin. The right liver lobe was not palpable. There was no diarrhea. During the first week the temperature rose to 102.2 F. As

the stomach X ray was suggestive of an abscess of the left liver lobe, chloroquine, oxytetracycline, and later also emetine were given. The fever then dropped to subfebrile levels, the abdominal pain became less violent, but the tumor remained unchanged. Both blood sedimentation rate and leukocytosis increased. Eighteen days after admission to hospital the patient suddenly collapsed and was operated on when a perforation of the abscess was suspected. The left lobe of the liver was found enlarged and adherent to the anterior wall of the abdomen. On aspiration 250 ml of brownish, odorless, sterile pus were removed from the adherent part, and lipiodol and air were injected again for radiological follow-up. No parasites were found in the pus. The postoperative course was uneventful, and the patient recovered. X-ray examination of the liver showed an orange-sized cavity in the epigastric area with lipiodol at its base and air on top. The cavity gradually decreased in size.

Comment: This patient had a fairly recent history of diarrhea with blood and consequently developed signs of an acute abdomen. A tumorous mass was found in the epigastrium, and the liver filled the left hypochondrial space. Blood sedimentation rate and leukocytes were increased, and the Weltmann coagulation band was extremely short. All these signs are typical of an amebic abscess of the left liver lobe, though no amebae were found in stools or in the pus from the abscess. The adhesions between the abscess and the abdominal wall suggested a walled-off perforation of the abscess into the peritoneal cavity.

The following four cases are given as summaries only. For additional details see Tables 1 and 2.

CASE 5

A 51-year-old woman, born in Hungary, allegedly had no previous illness such as diarrhea. One week prior to admission she suddenly fell ill with signs of an acute abdomen and subicterus. Later, an epigastric mass connected with the liver, increased blood bilirubin, and bile excretion in the urine were found. X-ray studies showed pressure on the stomach from right to left (Figure 4), and from front to back (Figure 3). On operation an abscess was found in the left lobe of the liver, adherent to the anterior wall of the abdomen. In spite of the fact that no direct evidence was available to prove the amebic origin of the abscess, the



FIGURE 5. Lateral view of abdomen during barium enema. Forward displacement of descending colon and splenic flexure by left lobe abscess (Case 6). Line indicates air on top of abscess.

acceptance of such an origin appears justified on the following grounds:

1. No other primary infection, such as bacterial focus, was found in the abdominal cavity.
2. The thick, brownish-green pus was odorless and sterile. Amebic abscesses without the characteristic appearance of "anchovy-paste" were described by Lamont et al. (4) and Paul (5).
3. The patient recovered rapidly after operation and subsequent antiamebic, though without antibiotic, treatment.
4. As has already been pointed out, in tropical and also in subtropical regions like Israel where amebiasis is endemic, liver abscesses with clinical signs like those described in this case are usually considered to be of amebic origin (5).

CASE 6

A 56-year-old male emigrated four years earlier from Roumania. There was no past history of diarrhea. For the preceding five years, and particularly so during the week prior to admission, he complained of postprandial epigastric pain. On chest screening the left diaphragm was immobile and air was noticed between liver and right diaphragm.

On physical examination the patient appeared to be seriously ill and was found to be subicteric. There was tenderness in the left hypochondrium.

Bilirubin appeared in the urine. Alkaline phosphatase and cholesterol were increased (see Table 2). Barium meal and barium enema showed a round shadow with fluid level underneath the left diaphragm, the size of an infant's head, pressing the descending colon in the region of the splenic flexure (Figure 5), and the stomach from back to front.

In view of the past history and the air found under the right diaphragm, a perforated peptic ulcer was suspected initially. On the other hand, the clinical course and later X-ray findings pointed in the direction of a left-sided, possibly retroperitoneal, abscess. On operation an abscess was found in the left lobe of the liver. The probability of an amebic origin was supported by the typical color of the sterile, odorless pus, and the prompt postoperative response to exclusively antiamebic treatment. The pressure on the stomach from back to front is explained by the position of the abscess in the upper lateral part of the left liver lobe. It cannot be excluded that the abscess perforated into the stomach at the time when the patient was admitted with signs of an acute abdomen, and at this or possibly a later stage into the peritoneal cavity as well. Such a course would offer an explanation for the air found in the abscess and under the right diaphragm.

CASE 7

A 26-year-old male emigrated six years previously from Iraq. There was no history of diarrhea. The patient was admitted with high fever and pain in the left hypochondrium and the left lower chest which radiated to the left shoulder. Considerable enlargement and tenderness of the left liver lobe, leukocytosis, an increased blood sedimentation rate, and an extremely shortened coagulation band (Weltmann) were found. On the third day of emetine treatment the patient began to recover. The symptoms and signs as well as the course of

the illness justify the clinical assumption that the patient suffered from an amebic abscess of the left liver lobe.

CASE 8

A 67-year-old male emigrated six years earlier from Iraq. He claimed to have been well until two weeks prior to admission when he developed rigors, pyrexia, severe epigastric pain, and diarrhea with blood and mucus. Apart from considerable epigastric tenderness and a tender left liver lobe, no additional abnormality was detected. In the feces, vegetative forms of *Entameba histolytica* were found. In spite of treatment with chloroquine and diiodohydroxyquin the patient died suddenly on the sixth day. Post-mortem examination revealed a generalized, fulminant amebiasis with multiple liver abscesses in an elderly malnourished man. The clinical syndrome, however, was dominated by signs and symptoms caused by a large left lobe abscess which eventually perforated into the peritoneal cavity.

CLINICAL DATA**AGE**

In this series the age ranges from 26 to 67 years, the average age being 52 years.

SEX

There were six males and two females. This proportion is in accordance with that found generally in hepatic complications of amebiasis.

SIGNS AND SYMPTOMS

Findings characteristic for abscesses of the left liver lobe are presented in Table 1. Pyrexia was found in all patients, while rigors were observed in only two. The left liver lobe or the liver as a whole was enlarged in seven, and there were pain and tenderness in the left hypochondrium and the epigastrium, or both, in six cases. In Case 2 the right liver lobe only was enlarged. Physical changes in the left thorax were found in three patients only, while pain radiating to the left shoulder occurred in two. Cough was symptomatic in three cases. Diarrhea with blood was a rare feature. Jaundice was a complication in three

TABLE 1. Diagnostic Criteria in Eight Cases

Clinical Features	Case							
	1	2	3	4	5	6	7	8
Major findings								
Pyrexia	+	+	+	+	+	+	+	+
Enlargement of liver or left lobe only	+(§)	+(§)	-	+(§)	+(§)	+	+	+
Proven left lobe abscess	+(+)	+	+	+(+)	+(+)	+(+)	0	+
Increased blood sedimentation rate	+	-	+	+	+	+	+	+
Short Weltmann coagulation band	+	0	+	+	-	+	+	0
Leukocytosis	+	Incomplete	-	+	+	+	+	+
Positive X-ray findings	+	+	+	+	+	+	Incomplete	Incomplete
Response to antiamebic therapy	+	Incomplete (x)	0(x)	+	0	+	+	Incomplete (x)
Minor findings								
Jaundice	-	+	-	-	+	+	-	-
Cough	-	+	+	+	-	-	-	-
Physical changes and pain in left chest	-	+	+	-	-	-	+	-
Vomiting	-	-	-	+	+	+	-	-
Rigor	-	+	-	-	-	-	-	+
Diarrhea with blood	-	-	-	+	-	-	-	+
<i>Entameba histolytica</i> in feces	0	+	-	-	-	0	-	+
Enlargement of cardiac dullness	-	-	+	-	-	-	-	-

0: Not investigated, or no proper antiamebic treatment given.

+: Abnormal findings, or response to treatment.

-: Normal findings, or no response to treatment.

Incomplete: Incomplete investigation, or incomplete treatment.

(§): Mass palpated in hypochondrium or epigastrium.

(+): Drainage of abscess.

(x): Died.

patients. In seven an abscess cavity was found in the left liver lobe. Four patients were given full antiamebic treatment; of these, three also were operated on. In one case an operation was performed but no specific drug therapy given. In two of the three patients who died, emetine injections were started only shortly before death. The third patient, though fully treated, succumbed to a fulminant infection with mul-

tiple small liver abscesses in addition to one big necrosis in the left lobe.

LABORATORY DATA (TABLES 1 AND 2)

While leukocytosis is a prominent feature, a normal white blood count was found in one patient. The blood sedimentation rate was increased, and Weltmann's coagulation band was shortened in all but one case. Feces examined in six patients were

TABLE 2. Liver Function Tests in Seven Cases

Case	Thymol Turbidity Normal: 0-5 u	Thymol Flocculation 0	Cadmium Sulfate Negative	Serum Protein A/G: 5/2*	Takata-Ara Negative	Serum Bilirubin 0-0.8 mg/100 ml	Cholesterol 150-250 mg/100 ml	Alkaline Phosphatase 3-5 u†	Remarks
1	7 u								
2						9			Hydrops of gall bladder
3			+	G>A					
4	10 u	3+							Bilirubin in urine
5				G>A	+	1.26			Bilirubin in urine
6	3 u					2.9	328	8.2	Bilirubin in urine
7		+	+						

Normal: Normal values.

*: A; Albumin, G; Globulin.

†: Bodansky units.

u: Units (Maclagan).

+: Positive.

positive for *Entameba histolytica* in only two. Complement fixation tests were not carried out. The results of the liver function tests (Table 2) are suggestive of parenchymatous damage in four patients (Cases 1, 3, 4, and 7), and of an obstructive lesion in three (Cases 2, 5, and 6). In Case 8 liver function tests were not carried out.

X-ray Findings: Lung radiography with particular attention to the right diaphragm is considered to be of appreciable diagnostic assistance in the detection of amebic involvement of the right liver lobe (1). In the case of left lobe abscesses, however, a final clinical diagnosis can be established only by more comprehensive X-ray investigation.

As these abscesses extend in the majority of cases into the abdominal cavity, pulmonary findings and diaphragmatic changes are comparatively infrequent. The radiologist's attention is therefore focused on the abdominal organs, particularly the stomach.

In this series barium meals were given to four patients, all of whom showed typical changes. In Case 6 the stomach was displaced forward, and in two patients (Cases 1 and 6), to the right (Figure 2). These changes indicated extension of the abscess toward the lesser sac and to the left. In Case 1 signs of pressure were seen on the upper part of the greater curvature (Figure 2), and the stomach was displaced backward (Figure 3). This abscess extended toward the anterior division of the left subhepatic space. The other two patients (Cases 4 and 5) showed changes as described by De Bakey and Ochsner (7), and by Miles (9), displacement backward (Figure 3) and to the left, causing a sickle-like appearance of the stomach (Figure 4). In these cases the abscess also spread toward the anterior division of the right subhepatic space.

A barium enema was performed in Case 6 where forward displacement of the splenic

TABLE 3. Radiological Findings

Organs Investigated	Cases Investigated	Positive Findings
Stomach	4	4
Colon	1	1
Left diaphragm	8	2*
Left lung and left pleura	8	3*
Pericardium	8	1

* In Case 4 diaphragmatic as well as pulmonary changes were found.

flexure by a big left lobe abscess was found (Figure 5).

A summary of the radiological findings in all cases is given in Table 3.

CONTENTS OF ABSCESS

The finding of necrotic material like "anchovy paste" is generally considered to be the most important diagnostic criterion for the amebic nature of pus from liver abscesses (4, 7). We saw such pus in only five cases (Cases 2, 3, 4, 5, and 6). In two cases the color was unusual (Cases 1 and 8), but the clinical syndrome seemed to justify our diagnosis. In Case 7 no exploration was performed.

The amebic origin of an abscess, however, is not excluded by a color different from the typical chocolate-brown pus (4, 5). Lamont et al. (4) found "typical pus" in only 43 of 106 patients, while in 36 cases its color appeared to be more indicative of a pyogenic abscess. The pus is sterile in uncomplicated cases and contains *Entameba histolytica* only occasionally (16).

FINDINGS AND COMPLICATIONS

The following changes were found on laparotomy (4 cases) and on post-mortem examination (3 cases):

1. Perforation of the abscess into the peritoneal cavity (Cases 2, 3, 6, and 8). One abscess burst into the suprarenal space (Case 3), and two into the lesser sac (Cases 2 and 6); the latter finally extended into the peritoneum generally.
2. Considerable enlargement of the left liver lobe (Cases 1, 4, 5, and 7).
3. Adhesions between the abscess and the anterior abdominal wall or the left diaphragm (Cases 1, 2, 4, and 5).
4. Perforation into the pericardial sac (Case 3).
5. Complete destruction of the left liver lobe (Case 2).
6. Inflammatory changes in the portal area (Case 2).

7. Atelectasis in the left lung (Case 3).
8. Metastatic brain abscesses (Case 3).

The anatomical position of the left liver lobe shows the possible extension of abscesses originating in this organ (Figure 1). This topography also explains the relative frequency of abscesses walled off by the lesser sac.

DISCUSSION

It is generally accepted that *Entameba histolytica* as well as other infective agents which inhabit the large intestine reach the liver via the portal vein (8, 17). The number of abscesses developing in the left lobe is considerably smaller than that occurring in the right liver lobe. According to Paul (5), De Bakey (7), Miles (9), and Shaw (13), left lobe abscesses are found in 6 to 33% of all liver abscesses. We found five such abscesses* in a total of 28 cases of amebic liver abscesses, an incidence of 18% during the last 11 years. Several theories have been offered in explanation of this statistical discrepancy.

Kean (18), in a series of 90 amebic abscesses of the liver, found four of them in the left lobe. The author concluded that the localization of the abscess does not depend on the intestinal region affected by the parasite. Elsberg (19) considers the more frequent occurrence of right lobe abscesses to be due to the greater width and the straight course of the right branch of the portal vein in contrast to that of the left branch. This topographic difference may well be compared with that between the course of the right versus the left bronchus, resulting also in a considerably larger number of abscesses in the right lung. Shaw (13) and Talbot (20) explain the relative infrequency of left lobe abscesses by the comparatively smaller volume of the left liver lobe. The most interesting interpretation has been suggested by Séregé (21) who

* The fifth patient was admitted after completion of this paper.

found that in the short portal vein separate currents of blood, each derived from a different tributary, existed side by side. In dogs, india ink injected into the superior mesenteric vein which serves the proximal colon is carried to the right liver lobe, while the dye injected into the inferior mesenteric vein is carried to the left lobe. It seems possible that in man, right lobe abscesses are being caused by more frequent, though less characteristic, and usually chronic changes in the cecum; the rarer acute dysenteric conditions of the recto-sigmoid colon, also being treated more vigorously, as a rule, lead to the more infrequent involvement of the left liver lobe (3).

As we demonstrated in our series, and as is also evident from the literature (9, 20), amebic abscesses of the left liver lobe are frequently not suspected prior to laparotomy or even before a fatality. On careful analysis of our material, we collected clinical, laboratory, and radiological data which appear to be helpful in arriving at an early diagnosis of this rare syndrome. Similar investigations have been carried out previously by others (4, 5, 18) with a view toward establishing the earliest diagnosis possible in amebic liver abscesses.

In all our surviving patients we found at least six of the eight major diagnostic features enumerated in Table 1. According to our experience it should be possible to establish an early diagnosis of amebic abscesses in the left liver lobe, provided this clinical entity is considered as one of the diagnostic possibilities in conditions localized in or around the left hypochondrium and the epigastrium, or both. Disorders of the stomach, the splenic flexure of the colon and its adjoining parts, the pancreas, the spleen, the left kidney, and the left pleura or lung therefore have to be excluded. Only rarely is the left liver lobe included in these considerations, although its weight is about 500 grams and it definitely belongs to this area (Figure 1).

The following are the principal conditions to be differentiated from abscesses of the left liver lobe:

1. Tumors, including echinococcus (9, 14-16).
2. Acute conditions accompanied by splenomegaly (16, 22).
3. Perforation of peptic ulcers (16).
4. Nonamebic left subphrenic abscesses.
5. Obstructive jaundice due to various causes.
6. Intestinal obstruction.
7. Left perinephric abscess.
8. Disorders of the lower lobe of the left lung or pleural space (11, 23).
9. Acute pericarditis (4, 14, 15, 24).

As a rule it is nearly impossible to arrive at a well-founded diagnosis of an abscess of the left liver lobe by physical examination only, unless a cyst-like mass moving with respiration is palpated in the left hypochondrium or the epigastrium. The diagnosis, however, has to be considered, particularly in tropical and subtropical regions, whenever a patient suffers from an acute or subacute condition in his left upper or his central abdomen.

Two complications are of particular interest, pericardial involvement and jaundice. As has already been stressed, left lobe abscesses in contrast to those of the right lobe tend to perforate more readily into abdominal structures. Takaro and Bond (15) found changes in the left chest in only 10% of more than 400 cases of amebiasis with pulmonary and pleural involvement. While right lobe abscesses often involve the right chest cavity, pericardial complications have been reported exclusively with left lobe abscesses (4, 7, 12-15). This observation has been explained by the fact that only the medial third of the left diaphragm is in direct contact with the left lobe of the liver. Cephalad to this area of contact lies the heart. Pericardial complications do not exclude additional peritoneal involvement (12, 15).

Three patients developed jaundice. Most authors consider icterus to be a rare complication of amebic abscess of the liver (11, 14, 25). Lamont et al. (4) found increased serum bilirubin in 19 of their 187 patients. These authors and Manson-Bahr (11) are of the opinion that the jaundice is due to occlusion of numerous intrahepatic bile ducts as a result of pressure exerted by a large hepatic abscess. As six of their 19 cases died, Lamont et al. consider icterus as indicative of poor prognosis, a conclusion we were unable to confirm in our small series of cases. The laboratory findings in Cases 2 and 6 support the assumption that the jaundice was obstructive. In these two cases the abscess extended clearly into the lesser sac which in its medial part has a common border with the common bile duct. A perforation of a left lobe abscess into the bursa omentalis, with pus filling this sac and thereby possibly obstructing the common bile duct from the outside, should therefore be suspected whenever an acute abdomen is noticed in such cases complicated by jaundice.

Deviation of tests pointing in the direction of parenchymatous liver damage are rarely found in amebic abscesses of the liver (4, 14). Lamont et al. (4) are of the opinion that disturbed liver function tests are of no particular importance in the diagnosis of liver abscesses. In spite of certain such deviations in six of our patients (Table 2), we too do not consider these changes to be characteristic for the underlying disorder, unless the tests point to an obstructive lesion. Abnormal liver function tests based on the derangement of serum protein fractions are comparatively frequent findings in our general patient population. However, the possibility cannot be excluded that a previously damaged liver might be more readily affected by amebic complications (11).

The mortality in solitary amebic abscesses of the liver, in general, varies from near 0 (16) to 11% (7). We were unable

to find reports on the mortality in left lobe abscesses exclusively. This, however, seems to be higher than in right lobe abscesses for the following reasons: The hidden localization of left lobe abscesses frequently causes a delay in diagnosis, contributing considerably to an increased fatality rate. Secondly, there exists this greater tendency of left lobe abscesses, in contrast to those of the right lobe, to extend into adjacent structures.

In this series there were three deaths. In Case 2 the correct diagnosis was established only on post-mortem examination. Case 3 died after perforation of the abscess into the pericardial sac, and the development of metastatic brain abscesses. Case 8 ran a clinical course typical of a left lobe abscess with perforation into the peritoneal cavity, though the ultimate downhill course was determined by unsuspected multiple liver abscesses in a malnourished patient. The mortality in such cases will decrease, if left lobe abscesses are suspected and treated at an early stage.

Treatment of amebic abscesses of the left liver lobe does not differ basically from that of liver abscesses in general. Combined application of emetine and chloroquine will probably cure a certain number of early acute cases, like Case 7 (4). If the diagnosis is reasonably certain and no improvement is evident on conservative treatment after one to two weeks, surgical intervention becomes imperative. Although needling of the left lobe of the liver has been advocated (4, 5, 12), we avoided this procedure for its apparent danger to adjoining structures. In addition, the possibility of entering an echinococcal cyst constitutes an ever-present risk.

SUMMARY AND CONCLUSIONS

An attempt is made to define the clinical syndrome of amebic abscess of the left liver lobe.

Anatomical differences between the two liver lobes seem to be essentially responsible

for the distinctly different clinical appearance with right versus left lobe abscesses.

An enlarged liver, particularly in its left aspect, in a febrile patient with severe pain in the epigastrium or the left hypochondrium, or in both, is a characteristic finding. On X-ray examination changes in stomach contour and position and pressure on the colon are characteristic and usually allow for an exact diagnosis. Left lobe abscesses have a particular tendency to perforate into neighboring abdominal structures. Extension into the pericardial sac has also been observed. Jaundice appears to be comparatively frequent when perforation into the lesser sac has occurred. This icterus is obstructive, and an explanation of its possible mechanism is offered.

In spite of the fact that patients may sometimes respond to conservative treatment only, we are of the opinion that the diagnosis of an amebic abscess of the left liver lobe constitutes an almost absolute indication for additional surgical intervention.

Reasons for the comparative rarity of left lower lobe abscesses are discussed. Proper evaluation of these factors might contribute to the understanding of the pathogenesis of left lobe abscesses as distinct from those of the right lobe.

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SUMMARIO IN INTERLINGUA

Es interprendite le tentativa de definir le syndrome clinic de abscesso amebic del lobo sinistre del hepate. Differentias anatomic inter le duo lobos del hepate pare serer responsabile pro le distinctemente differente aspectos de abscessos inter le lobo sinistre e le lobo dextere.

Un hepate allargate, particularmente in su aspecto sinistre, occurrente in un paciente fe-

brile con dolores sever in le epigastrio o in le hypochondrio sinistre o in ambe, es un constatacion characteristic de abscesso del lobo hepatic sinistre. In le roentgenogramma, alteraciones del contorno del stomacho e del position de illo, insimul con pression contra le colon, es datos characteristic e permitte usualmente le estableimento de un diagnose precise. Abscessos de lobo sinistre ha un tendencia particular de perforar se ad in le adjacente structuras abdominal. Extension ad in le sacco pericardial ha etiam esite observe. Jalnessa pare esser comparativamente frequente quando un perforacion ad in le sacco minor ha occurrite. Iste tipo de ictero es obstructive. Un explication possibile de su mechanismo es presentate.

In respecto del facto que il occurre que le paciente responde a un therapia conservatori, nos opinia que le diagnose de abscesso amebic del lobo hepatic sinistre representa un quasi absolute indication pro un intervention chirurgical additional.

Le rationes pro le raritate relative de abscessos del lobo sinistre es discutite. Le correcte evaluation de iste factores va possibilmente contribuer al comprehension del pathogenese de abscessos del lobo sinistre in contradistinction ab illos del lobo dextere.

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CASE REPORTS

Bacterial Endocarditis Due to *Pseudomonas Aeruginosa*

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WITH THE WIDESPREAD USE of antibiotics there has been an increase in the incidence of blood stream invasion by *Pseudomonas aeruginosa* has been noted (1). It is not surprising, therefore, that an increased number of cases of endocarditis due to this organism have been reported in the past few years.

To date, 12 patients with bacterial endocarditis due to *Pseudomonas aeruginosa* have been reported in the American literature; seven of these patients have been reported in the past eight years. Pre-existing heart disease, either congenital or rheumatic, was found in ten of these patients. All five of the patients with congenital heart disease developed the complication following open heart surgery with extracorporeal circulation (2). Two patients were narcotic addicts using nonsterile intravenous techniques (3, 4). Three patients developed the endocarditis following instrumentation or operation of the genitourinary tract at the time *Pseudomonas aeruginosa* was cultured from the urine (5-7). The most recent case to be reported occurred as a post-partum complication in a patient with severe rheumatic heart disease (8).

Only two of the patients previously reported survived. The first of these was reported in 1952 by Kenoyer, Stone, and Levin (9). The patient was a 20-year-old male known to have rheumatic heart disease. He was treated with neomycin in doses of 0.5 grams every six hours intramuscularly for 14 days. The second patient was re-

ported by Teitel and Florman (10) in January, 1960. Endocarditis occurred in a 14-year-old girl following the repair of an intra-atrial septal defect and patent ductus arteriosus with the use of extracorporeal circulation. Large amounts of polymyxin B were given over a four-month period, but blood cultures remained sporadically positive. Repeated surgical exploration of the heart with removal of an infected suture in the atria was followed by recovery of the patient.

CASE REPORT

A 20-year-old white female was admitted to the hospital on March 8, 1960, complaining of severe pain in her left foot and shoulder of three days' duration.

The patient had enjoyed good health until two weeks prior to admission when she developed a sore throat, stuffy nose, and diarrhea. A four-day course of chloramphenicol (250 mg four times a day) was given. Seven days prior to admission she noted pain, erythema, and tenderness of the right thumb, index finger, and two toes. Three injections of penicillin were given. The symptoms persisted. Sudden pain in her left foot, making weight bearing impossible, led to hospital admission.

No past history of heart disease or rheumatic fever was elicited. A tonsillectomy had been performed in April, 1959, and she had a tooth extraction late in 1959.

On physical examination the patient was noted to be a well-developed, well-nourished, white female weighing 110 pounds. The pulse was 85 per minute; blood pressure, 110/70 mm Hg; respiration, 18 per minute; and temperature, 98.4°F. She appeared pale, but alert and cooperative. No inflammation of the mouth or pharynx was noted. Cervical adenopathy was absent. The lungs were clear to percussion and auscultation. The heart was not enlarged. The rhythm was regular. The mitral sound was split, but no murmurs were heard. Tenderness was present in the right upper quadrant, but the liver was not enlarged. The spleen was not palpable. Resolving Janeway spots on the right thumb and index

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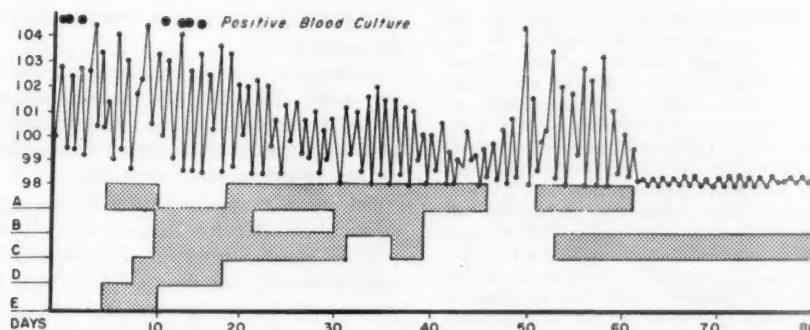


FIGURE 1. COURSE OF PATIENT WITH *Pseudomonas aeruginosa* BACTERIAL ENDOCARDITIS. A—POLYMYXIN B,
B—COLISTIN, C—SULFISOXAZOLE, D—KANAMYCIN, E—TETRACYCLINE.

finger pad, splinter hemorrhages on the left third, fourth, and fifth toes, and tenderness over the left acromioclavicular joint were present.

Admission Laboratory Studies: The hemoglobin was 10.1 g/100 ml; hematocrit, 33%; red blood cell count 3.5 million/mm³; white blood cell count, 9,000/mm³, with 57% polymorphonuclear leukocytes. The platelet count was 250,000/mm³. The urine contained a trace of protein. Electrocardiogram and chest roentgenograms were normal. The C-reactive protein was 2+.

Course: After blood cultures were drawn, therapy with intramuscular crystalline penicillin G, 6 million units, and streptomycin, 1 g daily, was instituted. The temperature, though normal on admission, fluctuated widely with peaks in the late afternoon reaching a high of 104.8°F by the fifth hospital day (Figure 1). The dose of penicillin was increased to 60 million units daily, administered intravenously. Sporadic splinter hemorrhages continued to appear. The entire length of the left clavicle became tender. A presystolic gallop at the aortic area with a split pulmonic second sound was noted.

On the sixth day the patient was lethargic. A relative bradycardia was observed. The white blood cell count had increased to 19,600/mm³ with a marked shift to the left. The next day a grade 2 systolic murmur was heard in the mitral area. The pulmonic second sound was widely split and a pericardial friction rub became audible. The murmur progressed to a blowing grade 4 murmur limited to the mitral area, over the next eight hours. Pain in both shoulders and arms developed. The blood pressure was 90/70 mm Hg, and the pulse was 120 per minute. The nail beds became cyanotic. An electrocardiogram at this time revealed an elevated S-T segment in lead I and aVL with depression of this segment in lead III. The precordial leads V₁ and V₂ were normal in configuration, but in V₃, V₄, and V₅ the R wave was no longer apparent in the QRS complex. Another electrocardiogram taken two days later showed inversion of the T waves in lead I and aVL. In

the precordial leads, a small R wave was present in V₁ but was absent in V₂ through V₅. There was definite elevation of the S-T segments in V₂ through V₆ with diphasic or inverted T waves in these leads. These findings were consistent with an anterior myocardial infarction possibly due to an embolus in a coronary artery.

Two blood cultures, taken shortly after admission, were reported at this time as positive for *Pseudomonas aeruginosa*, and the diagnosis of acute bacterial endocarditis due to this organism was made. The organism was inhibited by polymyxin B at 1.56 µg/ml, tetracycline at 3.12 µg/ml, and all of the sulfonamides at concentration of 1 mg/ml. The organism was resistant to all other antibiotics tested including neomycin.

Penicillin was discontinued and polymyxin B, 50 mg every six hours (3.65 mg/kg), was begun. Tetracycline, 0.5 g four times daily, was given orally. Cortisone, 350 mg, was administered intravenously because of the shock-like state. The cortisone was continued in smaller doses, decreasing 50 mg each day.

Slight improvement was noted, but on the eleventh day signs of meningeal irritation developed. A lumbar puncture revealed an opening pressure of 380 mm of water. The spinal fluid protein was 130 mg/100 ml; sugar, 62 mg/100 ml; and the cell count was 2,800/mm³, with 100% polymorphonuclear leukocytes. The culture was negative. Polymyxin B and tetracycline were discontinued. Colistin sulfate (30 mg intramuscularly every four hours), kanamycin (250 mg every 8 hours), and sulfisoxazole (2 g every 4 hours) were started. The temperature began to drop, and meningeal signs disappeared after two days. At this time the spinal fluid pressure was 140 mm of water, the protein was 22 mg/100 ml, and the cell count was 500/mm³. On the same day, however, the temperature spiked to 104°F. At this time a throat culture was positive for *Pseudomonas aeruginosa*.

Four of the six blood cultures taken during the six days of this therapy were positive for *Pseudomonas aeruginosa*. At this time polymyxin (200 mg

per day) was substituted for the kanamycin. All subsequent blood cultures were negative. On the eighteenth day gamma globulin was given, 20 ml initially and 10 ml every three days for a two-week period. The colistin sulfate was discontinued on the twenty-second day of hospitalization after a total dose of 2.16 g. The dose of polymyxin was reduced to 100 mg per day on the twenty-eighth day.

Coarsely and finely granular casts and 1+ proteinuria were noted before and throughout the course of the therapy. The blood urea nitrogen continued to rise reaching 57 mg/100 ml by the thirty-sixth day. At the end of seven weeks of hospitalization, the patient's weight had decreased to 80 pounds. After 32 days of negative blood cultures, all medications were discontinued. Following this the patient gained weight, and was subjectively and objectively improved. However, she remained febrile despite persistent negative blood cultures. On the fifty-first day the patient had a shaking chill. The temperature rose to 104°F. Polymyxin was reinstated, 100 mg per day, and continued for ten days. The fever gradually subsided. Blood cultures during this time remained negative. The patient's weight became stable. The blood urea nitrogen dropped to 5 mg/100 ml and the anemia did not progress. The white blood count remained normal. Protein, red blood cells, and casts disappeared from the urine.

At the time of discharge the patient's heart was not enlarged. A grade 3 blowing systolic murmur was present at the fourth intercostal space and at the apex. A thrill was present as well as a third heart sound in early diastole. The electrocardiogram was normal in configuration except for persistent inversion of the T waves and low amplitude R waves in the precordial leads. She was discharged on sulfisoxazole, 2 g per day, and has been followed for 12 months without evidence of recurrence.

COMMENTS

How this unusual pathogen entered the blood stream of this patient is obscure. Repeated cultures of the stool, urine, and vagina on admission to the hospital and throughout her hospitalization were negative. A history of recent tooth extraction and the persistent presence of *Pseudomonas aeruginosa* in throat cultures suggested the oral cavity as the likely source.

Another unresolved aspect of this case was the inability to culture the organism from the spinal fluid despite obvious signs and symptoms of meningitis. Three such cultures were negative. Although the patient was on therapeutic doses of antibiotics at this time, blood cultures were positive, but not the spinal fluid cultures. This finding has been noted in two of the 12 previously reported cases (4, 8). At subsequent autopsy in these patients, a pure culture

of *Pseudomonas aeruginosa* was obtained from the meninges.

Although myocardial infarction has not been previously reported in *Pseudomonas aeruginosa* bacterial endocarditis, the complication is a potential threat in any bacterial endocarditis regardless of the causative organism.

Polymyxin B appeared to be the therapeutic agent responsible for recovery of the patient (11). All blood cultures were negative during its administration. The dose employed was high; at one point 5.4 mg/kg were administered daily. A total of 6.5 grams of polymyxin B was given during a 47-day period. Transient toxic manifestations of the antibiotic noted included elevated blood urea nitrogen, anorexia, weight loss, and clouded sensorium. Other medications used concurrently with the polymyxin B may have been responsible for these findings. However, the symptoms persisted throughout the course of polymyxin B therapy, disappeared when the drug was discontinued, and recurred when it was reinstated.

The value of the colistin sulfate in the management of this case is difficult, if not impossible, to assess. The organism was sensitive to colistin originally. After six days of therapy with this agent, blood cultures were still positive, and the organism was no longer inhibited by colistin *in vitro*. Despite the failure of colistin sulfate, kanamycin, and sulfisoxazole to clear the blood stream, the meningeal symptoms present at the time this therapy was instituted disappeared within 48 hours.

The use of large amounts of gamma globulin in severe systemic infections is another therapeutic modality of disputed value (12). It is of interest, however, that seven of the previously reported cases were treated with polymyxin B in large doses, and all but one died. The one that survived did so only after surgical removal of an infected suture in the atria.

SUMMARY

A successfully treated case of *Pseudomonas aeruginosa* bacterial endocarditis, the third such reported, occurred in a 20-year-old white female with no previous evidence of heart disease. Of the various therapeutic agents used, polymyxin B seemed most responsible for the recovery of this patient.

SUMMARIO IN INTERLINGUA

Es reportate un caso, tractate a bon successo, de endocarditis bacterial causate per *Pseudomonas aeruginosa*. Iste caso es le terrie reportate in le litteratura. Le paciente esseva un feminina de racia blanc de 20 annos de etate. Previamente illa habeva monstrate nulle evidencia de morbo cardiac. Inter le varie agentes therapeutic usate, polymyxina B pareva esser primariamente responsabile pro le restabiliamento del paciente.

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Salmonella Pericarditis: Report of a Case and Review of the Literature

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PRIOR TO THE ANTIBIOTIC ERA, bacterial infection was one of the common causes of pericarditis. The incidence of bacterial pericarditis has decreased considerably with the use of antimicrobial agents. The organisms most frequently

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implicated are the pneumococcus, staphylococcus, hemolytic streptococcus, and tubercle bacillus (1-5). Pericardial involvement in salmonellosis is uncommon (4-5). It is the purpose of this paper to report and discuss the case of a child with salmonella septicemia and pericarditis and to summarize the previously reported cases.

CASE REPORT

A five-year-old white boy was seen for the first time at Children's Hospital on January 8, 1960. During the three to four months prior to admission

he had had sporadic episodes of leg and abdominal pain. Three weeks before admission a sore throat developed for which penicillin was administered with amelioration of the symptom. However, rhinorrhea, headache, fever, lethargy, severe nonproductive cough, and respiratory distress developed during the next week. A diagnosis of pneumonia was made, and treatment with parenteral and oral antibiotics was begun. Lethargy and irritability persisted, and for three to four days before admission the child refused to lie down to sleep because of dyspnea and abdominal pain. A pediatrician was consulted, evidence of cardiomegaly and heart failure was detected, and the child was admitted to the hospital. It was subsequently learned that approximately four months previously the child, while visiting a farm, had ingested well water and unpasteurized milk.

The past history, family history, and review of systems were noncontributory.

Physical examination revealed a well developed, irritable, acutely ill boy who was sitting upright in bed. His temperature was 102.8°F rectally, pulse 160 and weak, respirations 60, and blood pressure 104/60 mm Hg. There was a 10 mm Hg drop in systolic pressure during inspiration. His skin and mucous membranes were pale. The neck veins were distended in the upright position. The lungs were clear to auscultation and percussion. Although the cardiac apex impulse was palpable just lateral to the left mid-clavicular line, dullness to percussion extended from the mid-clavicular line on the right

to the mid-axillary line on the left. The rhythm was regular, and the rate was rapid. The heart tones were distant with a "tic-tac" quality. No murmurs or friction rubs were heard. The liver was enlarged to the level of the umbilicus and was tender. The abdomen was distended and tense. The remainder of the physical examination was negative.

The admission white cell count was 17,850/mm³ with 11% bands, 53% segmented neutrophiles, 25% lymphocytes, and 1% monocytes. The highest white cell count, obtained on the fifth hospital day, was 33,900/mm³ with a similar differential. The red blood count was 2,620,000/mm³; the hemoglobin, 7.9 g/100 ml; the sedimentation rate, 55 mm/hr; and the C-reactive protein, 4+. The stool was negative for occult blood. The admission urine specimen contained 50 mg/100 ml of protein but subsequent urinalyses were negative. The blood urea nitrogen was normal. Liver function tests were negative except for a total protein of 6.7 g/100 ml with an albumin of 2.3 g/100 ml and a globulin of 4.4 g/100 ml. The serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase were within the normal range.

An electrocardiogram (Figure 1) showed low voltage in the standard leads. The T waves were flat. There was upward coving of the S-T segments in the left precordial leads. Incomplete right bundle branch block was present. X rays of the chest (Figure 2) showed pronounced cardiomegaly without specific chamber enlargement. The vascularity

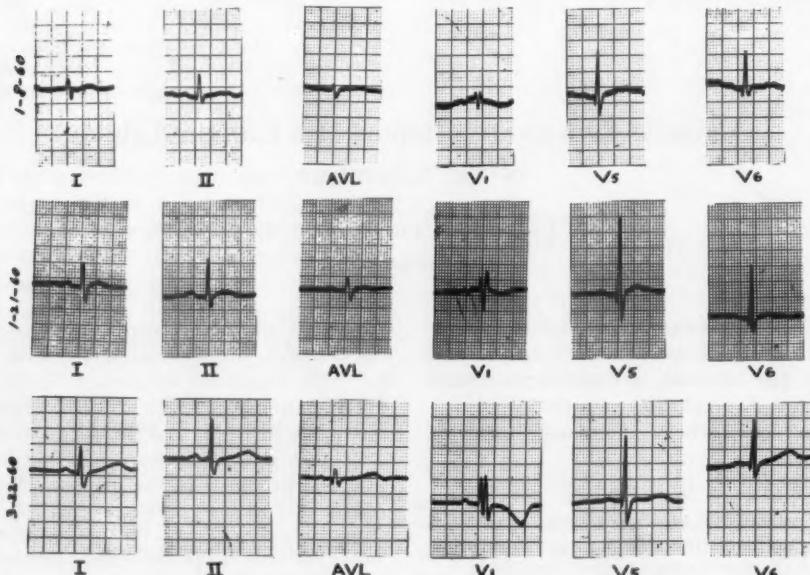


FIGURE 1. Electrocardiograms on January 8, January 21, and March 22, 1960, showing increasing voltage and loss of myocardial changes on serial tracings.

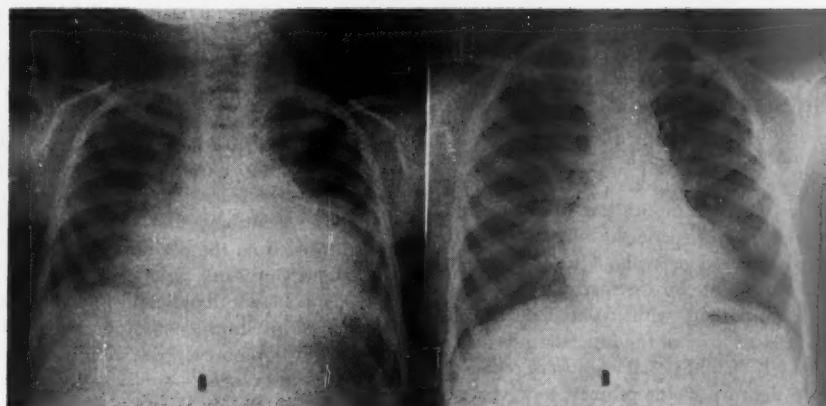


FIGURE 2. (a) Posteroanterior teleorontgenograms of the chest on admission, and (b) two and one-half months later.

was increased, and pleural fluid was present in the left costophrenic angle and along the left lateral chest wall. On fluoroscopy cardiac pulsations were poor. Hepatosplenomegaly was evident on films of the abdomen, and the clinical suspicion of ascites was supported.

The child remained acutely ill for the first five hospital days. His temperature spiked daily to 105°F rectally. Because of a positive throat culture for beta hemolytic streptococcus, penicillin was started with no clinical response. The child was given digitalis, but no improvement was noted. On the third hospital day a diagnostic and therapeutic pericardiocentesis was done using the left paraxiphoid approach. The pericardial sac was entered with a No. 20 needle without difficulty. Fifty milliliters of uniformly serosanguineous fluid were withdrawn. The fluid contained 36,000/mm³ red blood cells, and 1,550/mm³ white cells, as well as 2.5 g/100 ml protein. No organisms were seen on smear. On the following day a pericardial friction rub was heard for the first time. On the same day it was learned that the cultures of the blood, bone marrow, and pericardial fluid were growing a salmonella organism of the group C variety. Unfortunately, because of accidental loss of the specimens en route to the State Health Laboratory, the exact species was not determined. The patient's serum was found to agglutinate group C salmonella organisms at a titer of 1:256, and his own formalized organisms at a titer of 1:320. Stool cultures were negative. The boy was started on chloramphenicol, 750 mg daily, and demethylchlorotetracycline, 90 mg daily, as well as prednisone, 100 mg daily initially. Within several hours after the institution of steroid therapy the temperature fell from 105°F rectally to 102°F rectally, and by the following day it was normal. The patient's clinical appearance also changed dramatically with a de-

crease in his lethargy and irritability and an increase in his appetite. A blood transfusion was given because of his anemia. The dosage of prednisone was decreased rapidly after the initial defervescence, and was discontinued after five days. Following this there was a slight temperature elevation to 101°F rectally which subsided after three days. Penicillin, chloramphenicol, and demethylchlorotetracycline were continued. Over the four-week period following the institution of therapy the liver became smaller and nontender, the heart tones improved, and the abdominal distention, orthopnea, and friction rub disappeared. Digitalis was discontinued late in the hospital course without apparent adverse results. The electrocardiogram continued to show the S-T, T wave changes, but the voltage improved (Figure 1). On subsequent chest X rays, the heart size decreased moderately but did not return to normal. The pulmonary congestion abated, and the pleural effusion disappeared. Repeat blood cultures were negative, and chloramphenicol and demethylchlorotetracycline were discontinued after four weeks of therapy. The child was discharged to a convalescent home after 32 days of hospitalization.

When seen one and one-half months after discharge he was completely asymptomatic. There was no clinical cardiomegaly, the heart tones were normal, and the rate was 88. No murmurs or friction rubs were present, the abdomen was soft, and the liver no longer palpable. On a repeat electrocardiogram (Figure 1), the incomplete right bundle branch block persisted. The S-T segments and voltage had returned to normal, and the T waves in V5 and V6 were upright. Repeat chest X rays (Figure 2) showed a dramatic decrease in heart size. Salmonella agglutination tests on the convalescent serum were negative.

DISCUSSION

Cardiac involvement associated with salmonella infection has been recognized for many years. Myocarditis (6, 7) in the course of typhoid fever is not uncommon, and endocarditis due to typhoid (6), and other salmonella species (8) has been well documented. Pericarditis is an infrequent cardiac complication of salmonella disease. The early experience with this entity was entirely limited to typhoid fever. Volz, in 1844, was responsible for the first report of pericarditis in a patient with typhoid fever (9). During the latter part of the nineteenth century approximately 40 additional cases were reported (10). Since the turn of the century, however, reports of typhoid pericarditis have been sparse. Raybaud-Saillet (7) described a case of hemorrhagic pericarditis discovered at autopsy in a patient dead of typhoid fever. Norman and Ainsworth (11) reported a case in which *Staphylococcus aureus* pyopericardium complicated typhoid fever, and Woodward, Hall, Dias-Rivera, Hightower, Martinez, and Parker (12) mentioned one patient who developed a friction rub during a typhoid fever recurrence. Stuart and Pullen (13), and Eliakim (14) reported a total of four instances in which the electrocardiogram suggested pericarditis in typhoid patients with no symptoms or signs of this complication. Thiodet, Fourrier, and Arroyo (15) were able to aspirate pericardial fluid in two similar cases. In only one instance was the organism cultured from the pericardium either during life or after death, this being accomplished by Bacaloglu (6), in 1900, who isolated the typhoid bacillus at autopsy from the pericardium of a patient with typhoid endocarditis and pericarditis.

NONTYPHOID SALMONELLA PERICARDITIS

The first case of nontyphoid salmonella infection associated with pericarditis was reported by Cohen, Fink, and Gray (16) in 1936. Septicemia with *Salmonella choleraesuis* in a 36-year-old woman was accompanied by pneumonia, sterile pleural effusion, and a pericardial friction rub. Pericardiocentesis yielded ten milliliters of hemorrhagic fluid which were not cultured. The patient recovered. Cobley and Wilson (17) described a 34-year-old man who survived *Salmonella blegdam* septicemia and

cardiac tamponade necessitating repeated pericardial taps and finally a pericardiotomy. Culture of the fluid on several occasions was positive for the organism. Angrist and Mollov (18) discussed the case of a 60-year-old man with chest pain, diabetes, and coma who died before the correct clinical diagnosis could be made. Cholangitis and suppurative pericarditis were found at autopsy, and *Salmonella newport* was cultured from the pericardium.

Clément, Gerbeaux, Salet, and Chavelet (19) described a 14-month-old child in whom clinical evidence of pericardial effusion prompted several pericardiocenteses. Pericardial and pleural fluid cultures grew *Salmonella typhimurium* although blood cultures were negative.

Hennigar, Thabet, Bundy, and Sutton (20) reported the autopsy findings in a two-year-old boy who died suddenly during therapy for *Salmonella typhimurium* septicemia. A clinically unsuspected fibropurulent pericarditis with 20 milliliters of cloudy, yellow fluid was discovered. Endocarditis, myocarditis, and coronary arteritis were also present, and thrombosis of the posterior descending coronary artery had resulted in a posterior wall infarction. Gram-negative organisms were seen on histological examination of the myocardium, but no postmortem cultures were taken.

Demanet (21) described the case of a 64-year-old man with positive stool and pleural fluid cultures for *Salmonella typhimurium*. Pericarditis was manifested by cardiomegaly, a pericardial friction rub, and low voltage on the electrocardiogram. Atrial flutter with 2:1 block suggested concomitant myocardial involvement. The necessity of pericardiocentesis did not arise and recovery was complete.

Thiodet et al. (15) suspected pericardial involvement in a 24-year-old patient with *Salmonella paratyphi A* septicemia on the basis of electrocardiographic phenomena, despite the absence of clinical manifestations. Pericardial puncture yielded a few milliliters of sterile serofibrinous fluid. The patient recovered.

The child described in the case report above represents the eighth reported case of pericarditis associated with nontyphoid salmonella infection. The pertinent information concerning these eight cases is summarized in Table 1. The patients ranged in age from 14 months to 60 years. Five of the patients were male, two

CASE REPORTS

TABLE 1. Summary of Clinical and Pathologic Data in Eight Reported Cases of Nontyphoid *Salmonella* Pericarditis

Author and Year	Age and Sex	Organism	Site of Culture	Time of Diagnosis of Salmonellosis	Time of Diagnosis of Pericarditis	Findings of Pericarditis	Pericardial Fluid	Associated Cardiac Lesion	Treatment	Outcome
Cohen, Fink, and Gray (16) 1946	36/F	<i>Salmonella choleraesuis</i>	Blood	Ante-mortem	Ante-mortem	Friction rub	10 ml hemorrhagic fluid	1 degree heart block	None listed	Recovery
Cobley and Wilson (17) 1946	34/M	<i>Salmonella begam</i>	Blood Pericardial fluid	Ante-mortem	Ante-mortem	Friction rub	No culture	Mycarditis (?)	Sulfadiazine and sulfa-pyridine	Recovery
Angst and Mollov (18) 1946	60/?	<i>Salmonella newport</i>	Pericardium (autopsy)	Autopsy	Autopsy	None	Repeated taps	Purulent fluid	Penicillin and streptomycin intraperitoneally	Recovery
Clement, Gerbeaux, Salet, and Chavet (19) 1949	14 months M	<i>Salmonella typhimurium</i>	Pleural fluid Pericardial fluid	Ante-mortem	Ante-mortem	Friction rub	Purulent fluid	Positive culture	Penicillin and sulfa-streptomycin intraperitoneally	Recovery
Hennigar, Thubet, Bundy, and Sutton (20) 1953	2/M	<i>Salmonella typhimurium</i>	Blood Rectum	Ante-mortem	Ante-mortem	Poor tones	Galloping sound	Cardiomegaly	Chloramphenicol	Death
Demanet (21) 1957	54/M	<i>Salmonella typhimurium</i>	Stool Pleural fluid Bile	Ante-mortem	Ante-mortem	Friction rub	No culture	Coronary arteritis with thrombosis	Endocarditis Myocarditis	Death
Thiodet, Fourrier, and Arroyo (15) 1960	24/F	<i>Salmonella paratyphi A</i>	Blood	Ante-mortem	Ante-mortem	Friction rub	No tap	Flutter with 2:1 block	Chloramphenicol and streptomycin, and chloramphenicol intrapleurally	Recovery
Levin and Hosier 1960	5/M	Group C <i>Salmonella</i>	Bone marrow Pericardial fluid	Ante-mortem	Ante-mortem	Low voltage S-T, T wave changes	5 ml serofibrinous fluid	Mycarditis (?)	Chloramphenicol and demethylchlor-tetracycline Prednisone	Recovery

female, and in one the sex was not specified. The diagnosis of salmonellosis was made during life in seven cases, and of these, the diagnosis of pericarditis was made ante-mortem in six. The most common physical sign was a pericardial friction rub (five cases), and the next most common was cardiomegaly (four cases). Cardiac tamponade was present in three cases including our own. Pericardiocentesis was performed in five patients with positive pericardial fluid cultures in three. Of the two clinically unsuspected cases, the organism was isolated from the pericardium at autopsy in one. The pericardial fluid was purulent in three cases, hemorrhagic in two cases, and serofibrinous in one. Myocarditis was concurrently suspected in three cases, and proved at autopsy in one other. It is our feeling that myocarditis was likely in our patient. The pulmonary congestion, evidence of left heart failure, and the slow decrease in heart size despite dramatic improvement in heart tones and electrical voltage tend to support this contention. Antimicrobial therapy was employed in six of the seven patients with a clinical diagnosis of salmonellosis. Therapeutic pericardiocentesis was performed in three patients, and pericardiotomy was necessary in one. Two deaths occurred in this group of eight patients, and in both of these, the diagnosis of pericarditis was unsuspected during life. This suggests the advantage of early recognition and treatment of salmonella septicemia and pericarditis.

The species of *Salmonella* cultured from the seven previously reported patients varied. *Salmonella typhimurium* was isolated in three cases, with *Salmonella choleraesuis*, *Salmonella blegdam*, *Salmonella newport*, and *Salmonella paratyphi A* isolated in one case each. The organism cultured from the blood, bone marrow, and pericardial fluid in our case was found to belong to group C. Unfortunately, because of loss of the specimen, the exact species was not determined. Interestingly enough, a leukemic patient in the adjacent crib, who was admitted afebrile several days after our patient, developed fever on the eighth day of hospitalization. *Salmonella choleraesuis*, variety *kunzendorf*, was cultured from several blood specimens. It is probable, but unproven, that salmonella septicemia in the leukemic patient was the result of cross infection in hospital with our case as the source.

Smadel, Levy, and Diercks (22), and Woodward et al. (12) in 1951 described rapid symptomatic improvement in patients acutely ill with typhoid fever when cortisone was used alone or in addition to chloramphenicol. Defervescence and clinical improvement occurred frequently within the first 24 hours after the institution of therapy, whereas in the group treated with chloramphenicol alone, clinical response was often delayed three to five days. No adverse effects from cortisone therapy were noted. In our patient the temperature began to fall within several hours of the first dose of prednisone, and returned to normal within 24 hours. Symptomatic improvement was likewise rapid. Prednisone dosage was rapidly decreased as soon as an adequate response was assured, and it was discontinued after five days. No complications of steroid therapy were observed.

SUMMARY

A child with salmonella septicemia is described in whom the predominant clinical manifestations were related to associated pericarditis and, possibly, myocarditis. Group C *Salmonella* was cultured from the pericardial fluid. The previously reported cases of salmonella pericarditis are reviewed. The use of steroids as an adjunct to antibiotic therapy is briefly discussed.

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We are indebted to Dr. Dorothy Falkenstein for permission to report this case, and to Drs. Warren E. Wheeler, William O. Robertson, and Joseph M. Ryan for their helpful suggestions in the preparation of the manuscript.

SUMARIO IN INTERLINGUA

Es presentate le caso de un puer de cinque annos de etate qui suffreva, deposit tres septimanas, de rhinorrhea, mal de capite, febre, lethargia, tusse, angustia respiratori, orthopnea, e dolores abdominal. Le examine physic revelava un acutemente malade juvene in stato febril con le signos classic de effusion pericardial e un leve tamponage cardiac. Le constataciones radiologic e electrocardiographic supportava le diagnose clinic. Un pericardiocentece produceva 50 cm³ de liquido serosanguinose. *Salmonella* typo C esseva identificate in culturas ab sanguine, medulla ossee, e liquido pericardial. Tests de agglutination in

le sero esseva positive. Un melioration rapida e un restabilimento apparente resultava ab le tractamento con chloramphenicol, dimethyl-chlortetracyclina, e un breve curso de prednisona.

Durante le secunde medietate del dece-nono seculo, approximativamente quaranta casos de pericarditis typhoidic appareva in le litteratura medical. Depost ille tempore, cinque casos additional ha esseite reportate. In solmente un de iste casos le organismo esseva culturate ab le cavitate pericardial, e isto esseva effectuate al necropsia.

Le presente reporto es le octave de un caso de infection per un salmonella non typhoidic, associate con pericarditis. In sex del octo casos in iste gruppo, le diagnose esseva facite ante morte. In omne le sex, le paciente superviveva. Le duo casos que non esseva diagnosticate a bases clinic se terminava in le morte del paciente. Le organismo esseva culturate ab le pericardio durante le vita del paciente in tres casos e al necropsia in un caso additional. Le species de salmonella culturate ab le septe pacientes in le reportos ante le presente esseva *Salmonella typhimurium* (tres vices) e *Sal. choleraesuis*, *Sal. blegdam*, *Sal. newport*, e *Sal. paratyphi A* (un vice cata un). Le exacte specie in nostre caso non esseva determinate, sed *Sal. choleraesuis* var. *kunzendorf* esseva suspicite. Un breve discussion es includite in re le avantage de un combinante therapia a antibiotico e steroide.

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Unusual Manifestations of Syphilitic Cardiovascular Disease

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THE SALIENT CLINICAL AND PATHOLOGICAL FEATURES of syphilitic cardiovascular disease are well known, yet a unique case may still pose perplexing and intriguing problems. In the case reported, myxomatous degeneration of the cardiovascular connective tissue is the notable pathological finding. Myxomatous material, a normal body constituent, accumulates with increasing age and in certain pathological conditions in the heart and blood vessels (1, 2). The purpose of this report is to stress the anatomical and functional significance of myxomatous degeneration in syphilitic cardiovascular disease.

CASE REPORT

A 36-year-old sanitation worker was referred to this hospital because of "arthralgia." He had no history of venereal diseases. His polyclinic record revealed that four years previously a positive Wassermann reaction had been found on routine examination. Several courses of penicillin were instituted, but each was interrupted by the patient, and the Wassermann reaction remained positive. His wife and six children were healthy, and his wife's Wassermann reaction was negative. He enjoyed good health until six weeks prior to admission, at which time he began to complain of pain and swelling of the ankles. Two weeks later pain radiating along the thighs and legs developed. During the week prior to admission he had fever up to 39°C.

Physical examination revealed a well-nourished man in no acute distress. The pupils were round and equal, reacting normally to light and accommodation. The heart was enlarged to the left; no thrills were felt. A grade II systolic murmur and a diastolic Austin Flint murmur were heard at the apex. A high-pitched, blowing diastolic murmur was audible over the base of the heart and along the sternal border. The blood pressure was 120/40 mm Hg. Carotid arterial pulsations were prominent.

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The radial pulse was regular at 100/min, and of a water-hammer quality. The electrocardiogram showed left ventricular strain. The lungs were clear to percussion and auscultation. Liver and spleen were not enlarged. Slight pitting edema and tenderness were found at the ankles, and there was clubbing of the fingers and toes. There were no joint deformities, and movements were free. Neurological examination was negative.

Laboratory Findings: Erythrocyte sedimentation rate was 90 mm in one hour; hemoglobin, 8.5 g/100 ml; red blood cells, 3,600,000/mm³; white blood cells, 5,500/mm³ with a normal differential count. Blood urea nitrogen, 24 mg/100 ml; cholesterol, 107 mg/100 ml. Serum total proteins were 6.3 g/100 ml, with an inverse albumin:globulin ratio; electrophoresis showed 29 to 35% gamma globulins. Liver function flocculation and turbidity tests were pathological. No lupus erythematosus cells were found on repeated examination of blood smears. Urinalysis disclosed traces of albumin and 10 to 15 red blood cells per high power field. The Rose-Waaler test and the latex fixation test were positive in a dilution of 1:128 and 1:640, respectively. The Wassermann, the Venereal Disease Research Laboratory reactions, and the Nelson Treponema pallidum immobilization test were positive. Numerous blood cultures remained sterile. The sternal bone marrow revealed normal hematopoiesis and an increase in plasma cells. The cerebrospinal fluid was normal, and the Wassermann reaction was negative.

X-ray Findings: X rays revealed enlargement of the left ventricle, and widening, as well as prominent pulsations of the thoracic aorta. The lungs were normal. There was roentgenologic evidence of periosteal new bone formation along the distal part of the right fibula, both tibiae, and left femur. There were no joint deformities.

Syphilitic cardiovascular disease was diagnosed. However, subacute bacterial endocarditis could not be ruled out in view of persisting unexplainable fever, anemia, constant microscopic hematuria, a gradually enlarging spleen, and clubbing. A combined three-week course of penicillin, 2,400,000 units, streptomycin, 1 to 2 g, and probenecid, 2 g daily, was instituted. The temperature decreased, but the patient's general condition deteriorated progressively. In the eighth week, congestive heart failure was apparent with increasing ankle edema, enlargement and tenderness of the liver, moist rales over the lungs and production of frothy, often blood-stained sputum. He was markedly dyspneic and cyanotic. Chest radiography revealed hilar enlargement and patchy infiltrations, mainly in the

right middle and lower field. Initially he responded satisfactorily to digitalis and diuretics. The serological tests for syphilis remained positive, but the patient declined further treatment.

In the sixteenth week uremia and jaundice developed. Blood urea nitrogen increased to 158 mg/100 ml; the urine contained small amounts of albumin, many red blood cells, granulated and hyaline casts; blood bilirubin was 5 mg/100 ml, of which 3.5 mg/100 ml were direct reacting; serum glutamic oxaloacetic transaminase was 540 units. In the eighteenth week the patient complained of a sudden onset of severe chest pain and breathlessness. A loud, harsh, pansystolic murmur, heard at the apex for the first time, was suggestive of rupture of the mitral chordae tendineae. Congestive heart failure progressed rapidly, and the patient died within ten days, 139 days after admission.

NECROPSY

The body was that of a well-nourished man. There was moderate edema. The skin and conjunctivae were icteric, as were the internal organs. Fibrous adhesions obliterated the right pleural cavity; remnants of the partially obliterated left cavity contained 250 milliliters of serous fluid. The lungs were bulky, heavy, firm, and uncollapsible. The cut surface was russet brown in color. A tenacious reddish exudate covered the bronchial mucosa. The thyroid and parathyroid glands were normal.

The pericardial sac contained 150 milliliters of serous fluid. The epicardium was flecked with small, opaque, greyish spots. The heart weighed 490 grams. All chambers were dilated. The walls of the left and right ventricles averaged 1.3 and 0.6 centimeters in thickness. The myocardium was studded with numerous scars, 0.1 to 2 centimeters in diameter. The aortic and pulmonic orifices were dilated. There was widening of the commissures of the aortic cusps. The aortic and mitral cusps were slightly thickened. The posterior mitral leaflet was retracted consequent to rupture of its chordae tendineae (Figure 1). A few reddish-grey vegetations were adherent to the ventricular surface of the mitral valve and to the chordae tendineae near their attachment to the leaflets. The pulmonary and tricuspid valves appeared delicate. The coronary arteries were within normal limits, and the coronary ostia were patent.

The ascending aorta and aortic arch were fusiformly dilated. The intima exhibited raised, irregular, opaque, greyish-white plaques with longitudinal wrinkling and furrowing. The ad-



FIGURE 1. Left view of the heart. Retraction of the posterior mitral cusp consequent to rupture of its chordae tendineae. Note the vegetations on the chordae near their attachment to the leaflet.

ventitia was somewhat thickened. The descending aorta and large arteries were normal.

There were 300 milliliters of serous fluid in the peritoneal cavity. Enlarged, soft, greyish lymph nodes were found in the mesentery and gastrohepatic ligament. The liver weighed 1,450 grams; the cut surface revealed red, pinpoint-sized central zones contrasting with a yellowish background. The extrahepatic biliary system was intact. The spleen was enlarged (290 grams) and congested; some small brownish spots were seen on the cut surface. The alimentary tract, pancreas, and adrenal glands were unremarkable. The kidneys were swollen (combined weight, 400 grams), the capsules stripped with ease, the surfaces were smooth, and the cortico-medullary junctions were well defined. The urinary passages and bladder were normal. There was no abnormality of the external or internal genital organs.

The brain, meninges, and pituitary gland were unremarkable. The distal half of the left tibia was removed and bisected. The cortex was surrounded by a thin and irregular, bone-hard layer.

HISTOLOGICAL FINDINGS

Multiple sections were taken from several areas of each heart chamber, and similar changes were found throughout. The myocardium was strewn with a multitude of scars, ranging in size from small, predominantly peri-

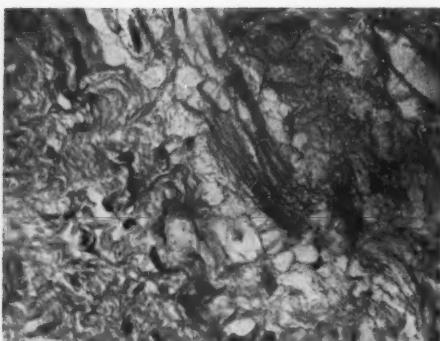


FIGURE 2. Myocardial fibers undergoing disintegration; the fibers are encroached upon by fibrous tissue and myxomatous material. Phosphotungstic acid hematoxylin $\times 240$.

vascular foci to the large, grossly noted cicatrices. The scars were composed of dense collagenous connective tissue, poor in cells and blood vessels, and containing but few elastic fibers. The compactness of the scars was interrupted here and there by small amounts of myxomatous material (see below). An accompanying chronic inflammatory reaction was conspicuous by its mildness. Many myocardial fibers were hypertrophic; there was no fatty degeneration. Single or grouped myocardial fibers, encroached upon by fibrous tissue or myxomatous material, were undergoing atrophy, degeneration, and disintegration (Figure 2). The large and medium-sized extramural and intramural coronary arteries were normal; a few small arteries and arterioles showed moderate to severe narrowing of the lumina by cellular intimal proliferation and fibrosis (Figure 3).

The outstanding microscopic feature was excessive and widespread occurrence of hema-toxyphil, stringy or amorphous material, either acellular or containing a few fibrocytes (hereafter referred to as "myxomatous"). It was distributed around the blood vessels and in the interstitial tissue, often causing separation of the muscle fibers from each other (Figure 4). There was occasional pooling of the material. The annulus fibrosus was extensively involved. A search for spirochetes in Levaditi-stained sections was unsuccessful. The mural endocardium and the epicardium were unevenly thickened, and large amounts of myxomatous material were present throughout. The epicardium

was focally infiltrated with lymphocytes, plasma cells, and histiocytes.

All four valves revealed myxomatous degeneration. The mitral valve was slightly infiltrated with lymphocytes, histiocytes, and fibroblasts. The vegetations consisted of thrombotic deposits containing no bacteria. In the chordae tendineae myxomatous degeneration was accompanied by mild fibroblastic proliferation.

The ascending aorta and aortic arch exhibited meso-aortitic alterations. The media was transversed in many places by fibrous scars; the elastic fibers were fragmented and decreased in number, and there was excessive accumulation of myxomatous material with occasional pooling. There was patchy thinning of the media deep to plaques of fibrous intimal thickening and atheromas. The adventitia was thickened by dense fibrous tissue, and many of its small arteries and arterioles were narrowed by intimal proliferation. Lymphocytes and plasma cells

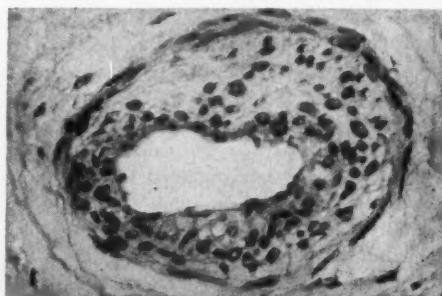


FIGURE 3. Cellular intimal proliferation and fibrosis in a small myocardial artery. Hematoxylin and eosin, $\times 240$.

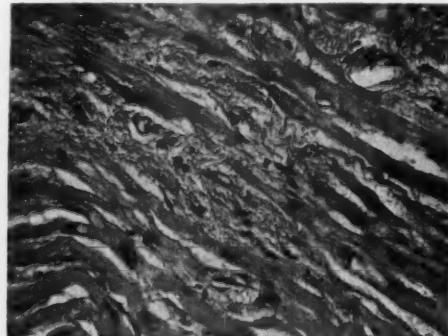


FIGURE 4. Separation of myocardial fibers by myxomatous material. Hematoxylin and eosin, $\times 240$.

were present around the adventitial capillaries, arterioles, and nerves. There were no granulomas and no spirochetes were demonstrated.

In the descending aorta, innominate, common carotid, and common iliac arteries, as well as in the pulmonary artery, myxomatous medial degeneration associated with elastic tissue destruction was observed, the changes decreasing in severity from proximal to distal. The adventitia of the proximal portion of the pulmonary artery was somewhat fibrotic and focally infiltrated by round cells; a few vasa vasorum were narrowed by intimal proliferation.

In order to establish the nature of the myxomatous material special techniques were employed. Van Gieson and resorcin fuchsin staining revealed solitary, distorted collagenous and elastic fibers within the material. The periodic acid-Schiff reaction was negative. With toluidine blue there was production of beta-metachromasia (Figure 5). The colloidal iron method gave an intense reaction. Alcian blue and

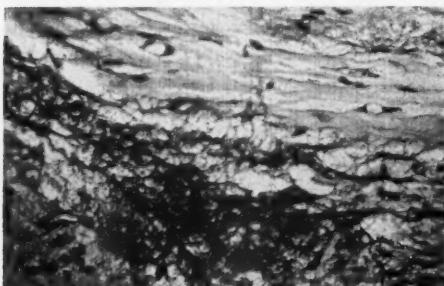


FIGURE 5. Metachromatic staining of the myxomatous material in the myocardium. Toluidine blue, $\times 240$.



FIGURE 6. Serial section of Figure 5. Complete reversal of metachromatic staining after three hours of hyaluronidase digestion. Toluidine blue, $\times 240$.



FIGURE 7. Microincineration of aortic media in region of aneurysm. Coarse mineral network and irregularly dispersed ash granules. Dark field illumination, $\times 200$.

methylene blue phloxine stained the substance blue and greyish-blue respectively. With phosphotungstic acid hematoxylin it appeared light yellowish with rare, tiny blue granules.

Representative sections of the myocardium, mitral valve, and aorta were subjected to hyaluronidase digestion. After deparaffination and hydration the slides were treated at 40°C with testicular hyaluronidase (Benger) 2 mg/100 ml, phosphate buffer of pH 5.8, and with the buffer solvent respectively. The slides were removed at one-hour intervals and stained with toluidine blue. The intensity of metachromatic staining in the buffer-treated sections, serving as controls, remained unchanged. After the third hour of digestion metachromatic substance was no longer present in the myocardium and valve (Figure 6), whereas in the aortic media only partial reversal of metachromatic staining was observed.

Since it was maintained that elastic tissue destruction and myxomatous degeneration were associated with reduction of the medial mineral content of the syphilitic aorta (3), microincineration was carried out. Our investigation did not confirm these assumptions. Unlike the normal delicate mineral framework of the aortic media of younger persons, a conspicuous increase in the ash content was found. The aortic media in our case contained a coarse mineral network with some irregularly dispersed ash granules (Figure 7).

The lungs showed thickened, cellular, and slightly collagenized alveolar septa. The alveoli varied in size; many were completely or partially occupied by fresh hemorrhages, accumula-



FIGURE 8. Low power view of lower half of tibia. The original cortex (right), containing enlarged marrow spaces, is separated by edematous connective tissue from the pseudocortex (middle). The latter is separated by dense connective tissue from a zone of an amorphous calcified mass (left). Hematoxylin and eosin.

tions of macrophages laden with hemosiderin, and some fibrinous plugs. The arteries and arterioles exhibited fibrous intimal thickening. Bronchopneumonic foci were present in the lower lobes.

The mucosa of the epiglottis and esophagus was infiltrated with acute and chronic inflammatory cells. The rest of the alimentary tract was unremarkable. There was severe liver congestion with centrilobular necrosis and midlobular fatty metamorphosis. In the spleen engorgement, distension of the sinuses, increase in connective tissue, and Gandy-Gamma bodies were found. The pancreas was normal. The lymph nodes showed reticuloendothelial hyperplasia and erythrophagocytosis; the dilated sinuses were filled with phagocytes, plasma cells, and neutrophilic and eosinophilic leukocytes. The kidneys revealed focal and diffuse thickening of the glomerular capillary basement membranes and glomerulocapsular synechiae. The epithelial cells of the distal tubules contained monorefringent fat droplets. The interstitial tissue was not increased or infiltrated. The testes and prostate were normal.

The central nervous system disclosed no abnormality. The pituitary, thyroid, parathyroid, and adrenal glands were unremarkable. The psoas muscle exhibited severe, predominantly segmental changes. There were fragmentation, homogenization, loss of cross striation, vacuola-

tion, fatty degeneration, and mild interstitial infiltration with lymphocytes and histiocytes.

A rib and a vertebra were of normal structure. The bone marrow was cellular; the reticulum cells were increased in number, and plasma cells were abundant. Examination of the tibia showed the features of hypertrophic pulmonary osteoarthropathy (4), namely, a so-called pseudocortex separated by edematous fibrous tissue from the original cortex. The latter contained large marrow spaces filled with fat tissue; distally, the cortex became progressively spongy in character. In addition, dense fibrous tissue, mildly infiltrated with round cells, separated the pseudocortex from an amorphous, calcified, band-like mass (Figure 8).

DISCUSSION

The diagnosis of syphilitic cardiovascular disease in this case is predicated upon the findings of positive serologic reactions, positive Nelson test, meso-aortitis, aortic aneurysm, and aortic regurgitation. Not all the lesions described above seem to be of syphilitic origin in the strict sense of the classical definition (5), but rather represent secondary manifestations, probably due to a hypersensitivity mechanism developing in the course of the syphilitic infection. Though the Wassermann reaction might have been a false positive, personal communication with authoritative serologists leads us to believe that the clinical and pathological picture in the presence of a positive Nelson Treponema pallidum immobilization test proves beyond reasonable doubt that the patient had indeed suffered from a syphilitic infection. Smith, Saxton, and Fritz (6) have reported on "syphilitic cardiovascular disease combined with chronic endocardial lesions usually attributed to rheumatic fever." In our patient the mitral valve was infiltrated with inflammatory cells, and vegetations were present. This valvular lesion is not necessarily rheumatic in origin. It is our opinion that it is reactive in nature, essentially a different expression of the same basic process affecting the cardiovascular connective tissue.

Brown induration of the lungs, pulmonary arteriosclerosis, and right heart hypertrophy are uncommon findings in syphilitic cardiovascular disease. Thus, it seems correct to consider an unusual process as the underlying cause. The outstanding feature in our case is the wide-

spread occurrence of myxomatous material in the heart and large arteries. This substance is characterized by its basophilia and metachromasia; it gives a positive reaction with colloidal iron and alcian blue; hyaluronidase digestion produces reversal of metachromatic staining. It is thus apparent that the myxomatous material consists of an acid mucopolysaccharide. Since it fails to stain with the periodic acid-Schiff reagent, it is probably composed of chondroitin sulphate (1, 3).

Myxomatous degeneration of the cardiovascular connective tissue is a feature of several disease entities. Among these Marfan's syndrome and Erdheim's idiopathic aortic medionecrosis are of prime importance. Apart from the presence of the myxomatous material in the cardiovascular system, none of the many other signs of Marfan's syndrome, such as arachnodactylia, subluxation of the lens, and various deformities, were present in our patient. Furthermore, wedge-shaped aortic medial scarring and adventitial obliterating endoarteritis, as were found in our case, are not characteristic for Marfan's syndrome and Erdheim's medionecrosis. In both, an inflammatory infiltration is present in the aortic media and adventitia, and the inner two-thirds of the media contains wide, thin-walled blood vessels. Similarly, other diagnostic possibilities, such as muscular dystrophy with cardiac involvement, and myxedematous heart disease, are unsupported from the clinical and pathological point of view.

Extensive myocardial scarring is known to occur in syphilitics; its cause is as yet controversial. The lesions are uncharacteristic, but Benda (5) considered the multiplicity of the scars in the absence of an obstructive vascular factor to point in favor of syphilitic "fibrous myocarditis." In our case the coronary ostia were patent, not being involved by the meso-aortitis. The coronary arteries were mostly normal, and though obliterating endoarteritis affected some small arteries and arterioles, the extent of the myocardial scarring was out of all proportion to the vascular changes present. The exclusion of all other possible agents is postulated by Saphir (7) to be the necessary condition for regarding myocardial fibrosis as luetic in origin. Since our patient suffered from no other disease which is known to cause myocardial scar-

ring, a causal relationship to the syphilitic infection must be implied.

Myxomatous degeneration of the heart and blood vessels occurs in various pathological conditions (3, 8), and is a part of the aging process (1). Myxomatous degeneration of the myocardium (7), valves, and aorta (9) has been described in syphilitics, but no untoward effects have been attributed to it. Bearing Serebrenikova's studies in mind (2), it may be assumed that in our case myxomatous degeneration of the myocardium, accompanied by loss of muscle tissue, progressed to scar tissue formation without an intervening phase of fibroblastic proliferation. However, it must be conceded that obliterating endoarteritis could have contributed to the myocardial cicatrization.

The cause of cardiovascular myxomatous degeneration in syphilitics is unknown. It seems that the cardiovascular system may be damaged in the course of a syphilitic infection by a mechanism analogous to that which presumably induces certain "collagen diseases" following streptococcal infection. A search for lupus erythematosus cells was repeatedly negative. However, the hypergammaglobulinemia, valvular vegetations, and renal as well as muscular changes are strongly reminiscent of such findings in many cases of various collagen diseases. Though not in themselves pathognomonic, they are identical with similar alterations encountered in certain diseases believed to be related to hypersensitivity reactions. Furthermore, they support our view that in the case presented herein, a syndrome suggestive of "collagen disease" developed in the course of, and secondary to, a syphilitic infection. Jaffé (10) regards luetic myocarditis as an allergic inflammation occurring in response to an antigen elicited by the syphilitic infection.

It cannot be established to what extent the aortic incompetence, myocardial scarring, and myxomatous degeneration of the heart contributed toward the chronic heart failure. In this connection the investigations of Fernex and Fernex (11, 12) are of special interest. These authors observed that myxomatous degeneration of the valves and annulus fibrosus produced mitral and aortic incompetence directly. In our case involvement of the annulus fibrosus and all valves apparently played a major role in causing both left and right heart failure. Fur-

thermore, the only plausible cause of the rupture of the mitral chordae tendineae is their myxomatous degeneration.

On admission the patient showed no signs of congestive heart failure; the slight ankle edema was probably part of the hypertrophic pulmonary osteoarthropathy (13). Overt cardiac decompensation did not develop until a few weeks later, and thereafter progressed rapidly. Rupture of the mitral chordae tendineae was the terminal event.

During the first few weeks of his illness the patient complained only of pain and tenderness in the lower extremities. The symptoms of hypertrophic pulmonary osteoarthropathy may precede the clinical manifestations of the intrathoracic visceral disease (13, 14). In the absence of objective signs of rheumatoid arthritis the accepted serological reactions are to be considered as false positives (15).

The described changes in the lower tibia, that is, the development of a pseudocortex, and of enlargement and fat tissue contents of Haver's system, are typical for hypertrophic pulmonary osteoarthropathy (4). Both the syphilitic cardiovascular disease and the brown induration of the lungs may have contributed toward its development. The significance and morphogenesis of the band-like mass of amorphous calcified material in proximity to the tibial pseudocortex is obscure. In the literature available to us it has been described neither in hypertrophic pulmonary osteoarthropathy nor in syphilis. A similar calcification has been observed following the experimental administration of fluorine (16). Hypothetically, it could represent a type of parosteal fibrous tissue damage caused by the same mechanism producing the cardiovascular, renal, and muscular changes.

SUMMARY

A case of syphilitic cardiovascular disease associated with extensive myocardial scarring and widespread myxomatous degeneration of the heart and large arteries is presented. It is assumed that cardiac myxomatous degeneration progressing to scar tissue formation in the myocardium was a major cause of chronic left and right heart failure as well as of rupture of the mitral chordae tendineae. Cardiovascular myxomatous degeneration might represent a form of connective tissue damage due to a hyper-

sensitivity reaction elicited by an antigen developing in the course of the syphilitic infection.

ACKNOWLEDGMENT

Our thanks are due to Mrs. K. Norton for the photographs and to Mr. Z. Shleifstein for technical assistance.

SUMARIO IN INTERLINGUA

Un masculo de 36 annos de etate esseva hospitalisate a causa de dolor e tumescencia in le region del cavilias e etiam a causa del presentia de febre. Le examine clinic revelava incompetencia aortic, allargamento del aorta thoracic, edema, e hyperesthesia del cavilias si ben que digitos hippocratic in manus e pedes. Significative constataciones laboratorial esseva un elevate sedimentation, anemia, e un invertite proportion albumina/globulina, con globulinas gamma amountante a usque a 35%, pathologia del tests de function hepatic, e positive serotests pro arthritis rheumatoide e syphilis, incluse le test de immobilisation secundo Nelson. Radios X del ossos longe monstrava neoplasia periosteal. Un tractamento antibiotic esseva institute. Tamen, le condition del paciente se deteriorava rapidemente. Congestive disfallimento cardiac, uremia, e jalessa se disveloppava. Le paciente moriva dece dies post que un diagnose de ruptura de mitral chordas de tendine esseva diagnosticata.

Le necropsia revelava aneurysmo aortic, meso-aortitis, incompetencia aortic, cardiomegalia, extense cicatrization myocardial, e marcata degeneration myxomatose del tissu conjunctive cardiovascular. Vegetations esseva presente super le valvula mitral. Le chordas de tendine posterior de ille valvula esseva rupturate. Le pulmones monstrava un grado sever de induration brun. Le cavitates serose contineva effusiones. Le organos interne esseva congestionate. Le membranas basilar glomerulo-capillari del renes esseva spissificate. Le musculo psoas exhibiva marcata alterations myositic. Le tibia monstrava hypertrophic osteoarthropathia pulmonar e—periphericamente—an amorphie bandiforme massa calcificate.

Apparentemente, degeneration myxomatose cardiaque, progrediente verso le formation de tissu de cicatrization, esseva un major causa de chronic disfallimento cardiac e de ruptura del chordas de tendine. Degeneration myxomatose cardiovascular representa possibilmente un forma de injuriation de tissu conjunctive como efecto de un reaction de hypersensibilitate evocata per un antigeno que se disveloppa in le curso del infection syphilitic. Le hypergammaglobulinemia,

le vegetaciones valvular, e le alteraciones renal e muscular supporta le conception que un tal reaction habeva occurrite in le presente caso.

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Erythrocyte Aplasia and Hypogammaglobulinemia

Response to Steroids in a Young Adult

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THE ANEMIA resulting from erythrocyte aplasia of the marrow with normal white cell and platelet development in the adult has been described in detail in a complete review by Tsai and Levin (1). A total of 27 patients was presented and reviewed, and mention was made of two additional patients from the Japanese literature.

This anemia is apparently one of a mixed group of primary refractory or aregenerative anemias with marrow pictures ranging from the

classical aplastic (empty) marrow in which all hemopoietic elements are virtually absent, to a hypercellular marrow (2). The marrow in pure erythrocyte aplasia is full and on first glance appears to be normal, with complete development of megakaryocyte and leukocyte precursors. On closer examination, it is noted that what appear to be normoblasts are lymphocytes, and that no red cell precursors are found on repeated scanning of the slides. Marked decrease or disappearance of only the erythrocytic elements from the marrow with normal white cell and platelet development has been reported in three groups of patients: [1] hereditary spherocytosis and other congenital hemolytic anemias in which an acute erythroblastopenia may super-

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vene (3), [2] congenital hypoplastic anemia of Diamond and Blackfan which is a disorder occurring in infancy (4), and [3] pure erythrocytic aplasia in adults as demonstrated in this report.

The association of erythrocyte aplasia and hypogammaglobulinemia was recorded in a case report published in 1956 by Ramos (5). This did not fit entirely the criteria of Tsai and Levin, since there was a leucopenia of 650 white blood cells/mm³. The patient did have a thymoma, however, which has been found in about 15% of adult cases with erythrocyte hypoplasia. This extraordinary coincidence of two rare entities, thymoma and erythrocyte aplasia, has received considerable discussion in the literature (6, 7). The additional finding of low gamma globulin which is actually an index of the presence and activity of its precursor cell, the plasma cell (8-11), suggests very strongly some common abiotrophy of the erythroid and probably the plasmacellular tissue. The virtual absence of plasma cells from the bone marrow and lymph nodes in cases of agammaglobulinemia in which they have been studied is strong evidence that plasma cells, or lymphocytes which appear to develop into plasma cells, are the major source of gamma globulin (8-11).

CASE REPORT

An 18-year-old unmarried Italian male was admitted to the Atlantic City Hospital on August 9, 1956, with complaints of marked weakness, palpitation of the heart, and shortness of breath. On June 18, 1956, approximately seven weeks prior to admission, he had had an upper respiratory tract infection for which he had received two injections of penicillin in a 24-hour interval. On June 26, he complained of weakness and fatigue; because of these symptoms, he discontinued his work as a bagger at a large chain grocery store. At this time, his physical examination was not remarkable except for moderate pallor of the mucous membranes. A complete blood count revealed a normocytic, normochromic anemia (3,030,000 red blood cells, 5,650 white blood cells/mm³, polymorphonuclears 34%, bands 3%, eosinophiles 5%, lymphocytes 51%, monocytes 7%). A study of the smear revealed an occasional macrocyte. There were no target cells, and the platelets appeared to be normal. Reticulocytes were 1%. The fragility test was within normal limits.

It was thought that the mild anemia might be due to the preceding infection and hematinic capsules (Trisicon) were prescribed. He failed to respond to this treatment, his anemia progressed, and he was admitted to the hospital.

The admitting physical examination revealed a white male in no distress, but with tachycardia and extreme pallor of the skin and mucous membranes. Temperature was 100F. The heart rate was 120 and a grade II systolic murmur was heard over the apex of the heart. The spleen and liver were not palpable. Extremities and neurological examination were normal. Laboratory studies on admission revealed 1,560,000 red blood cells/mm³, hemoglobin 3.6 g/100 ml, and 6,550 white blood cells/mm³. The smear revealed moderate hypochromia, but no macrocytes. Differential count was normal; erythrocyte sedimentation rate was 30 mm in 1 hour (Wintrobe). The fragility test, platelet count, bilirubin determination, Coombs' test, and lupus erythematosus preparation were all within normal limits, or were negative. Stools were negative for occult blood, and there was no other evidence or history of blood loss. A bone marrow aspiration from the iliac crest revealed aplasia of the erythroid series, with normal granulocytes and megakaryocytes. There were 5% eosinophilic forms. No plasma cells were seen.

Further questioning revealed no history of exposure to benzol derivatives or other agents known to be associated with aplastic anemia.

HOSPITAL COURSE

The patient received seven pints of blood during his hospital stay of 22 days. His hemoglobin rose to 11 g/100 ml, and his general condition improved. X ray of the chest, gastrointestinal series, and barium enema were reported to be negative. In particular, there was no suggestion of a thymic tumor.

A second bone marrow aspiration was made from the sternum before his discharge. Again there were no red cell precursors.

The patient was discharged from the hospital with a diagnosis of aregenerative anemia, or selective aplasia of the red blood cell series. Cobalt and iron (Roncovite) tablets, 1 four times a day, were prescribed. His hemoglobin gradually decreased at the approximate rate of 1 g/100 ml in seven days, and he was given whole blood transfusions every two weeks. There was no response to cobalt therapy. On September 20, 1956, this was discontinued, and prednisone, 5 mg four times a day, was prescribed. The patient was asymptomatic except for weakness.

Erythropoiesis as measured by reticulocyte appearance started on the twenty-eighth day, and a normal hemogram was recorded one month later, at which time prednisone was discontinued. This response is summarized in Figure 1. A bone marrow done on November 9, 1956, was normal. There were 1% eosinophiles and no plasma cells.

On May 8, 1957, a blood count revealed hemoglobin 14.6 g/100 ml, 4,970,000 red blood cells/mm³, 8,200 white blood cells/mm³, with a normal differential. The patient enlisted in the United States Air Force the following week. In December he began to experience chills, fever, general malaise, headache, and mild cough which he believed to be an attack of influenza. This lasted one week, but he

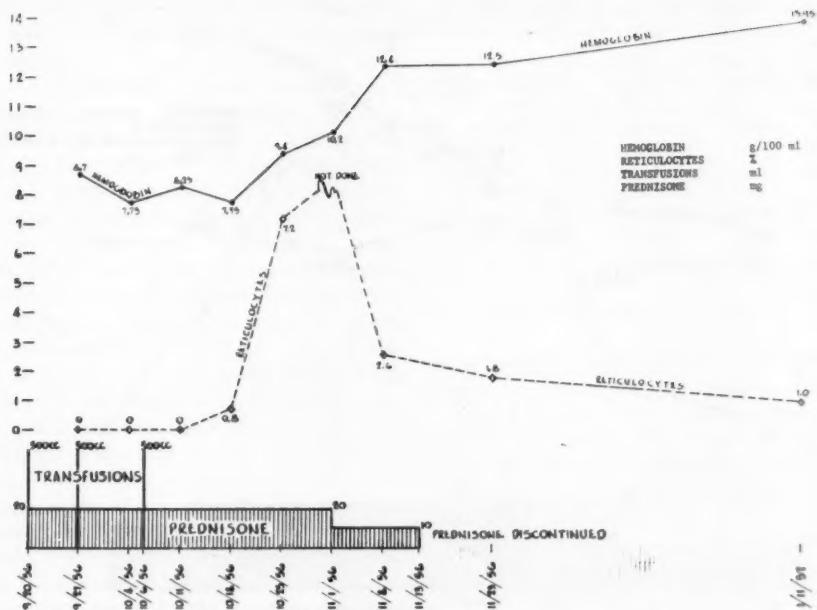


FIGURE 1. Hematologic response to prednisone.

continued to feel weak and fatigued and had some exertional dyspnea. He stated he had used cleaning fluid, type unknown, four to six weeks before in cleaning a desk.

He was admitted to Letterman Army Hospital on January 3, 1958. At this time, he was found to be pale, poorly nourished, and acutely ill. Pulse was 130 and regular. The liver was palpable 2 cm below the right costal margin, and the edge was firm and tender. The spleen tip was palpable on deep inspiration. There were no petechiae. He had a generalized, shotty adenopathy and the largest node measured 2 by 1.5 cm. The remainder of the examination was negative.

Laboratory studies revealed the following values: hemoglobin 4 g/100 ml; hematocrit 13%; 4,700 white blood cells/mm³; polymorphonuclears 52%, bands 4%, lymphocytes 24%, monocytes 16%, eosinophiles 4%, reticulocytes, absent. Sickle cell preparation was negative; serum bilirubin was 0.05 mg/100 ml in one minute, 0.4 mg/100 ml in 30 minutes. Coombs' test was negative; hemoglobin electrophoresis, A and A_s; no fecal hemoglobin; blood type AB; fecal urobilinogen 77 Ehrlich units/100 grams. One lupus erythematosus preparation was negative. Clot retraction was normal. Total serum protein was 5.4, with albumin 3.9, and globulin 1.5.

Serum electrophoresis was reported as albumin 48%, alpha₁ 6%, alpha₂ 14%, beta 17%, gamma 15%. An iron kinetic study revealed virtual absence of erythropoiesis and hemoglobin synthesis (12).

Bone marrow aspiration on January 10, 1958, revealed isolated erythroid aplasia. No mention was made of plasma cells or eosinophils.

A high level of urinary erythropoietin was found before and during remission, but none was found after recovery when the hemoglobin had returned to normal (13).

HOSPITAL COURSE

The patient received 2,300 ml of whole blood between January 5 and January 23, 1958. On January 14 he was started on crude liver, vitamin B-12, and pyridoxine parenterally, as well as folic acid and riboflavin by mouth, with no detectable response. On January 31 he was started on prednisone 12.5 mg four times a day. Serial reticulocyte count was zero until February 11, 1958, when it was recorded at 8.5%. It rose to a peak of 13.1%. Hematocrit rose from 20% to 33% after the reticulocyte rise. The patient was discharged from the service on May 1, 1958, and on May 7 he had the following blood count: hemoglobin 14.6 g/100 ml, 4,970,000 red blood cells, 8,200 white blood cells/mm³ with polymorphonuclears 68%, bands 4%, lymphocytes 20%, eosinophiles 4%, monocytes 4%. Reticulocytes were 1.6%; platelets were adequate on smear.

He remained on a maintenance dose of 2.5 mg prednisone twice daily until late in May, when he discontinued the medication. He was seen again on September 30, 1958, at which time he felt tired; he was found to have a recurrence of anemia. He

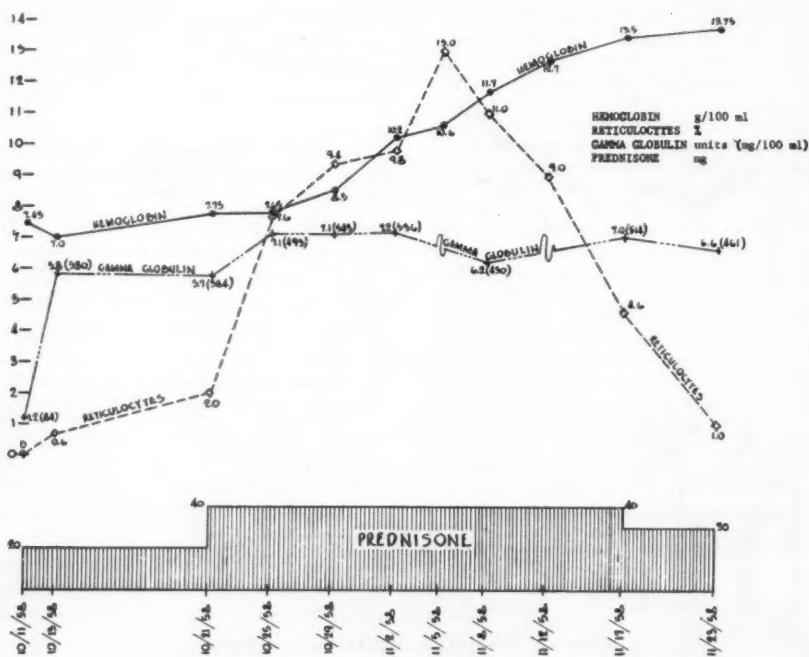


FIGURE 2. Hematologic and gamma globulin response to prednisone.

had been working as an electrical helper in a shop with a gasoline pump outside the door. He did not handle the gasoline. Physical examination was negative aside from the pallor.

Laboratory examinations at this time revealed hemoglobin 9 g/100 ml, 3,180,000 red blood cells, 4,200 white blood cells/mm³, differential normal, reticulocytes 0%. Serum electrophoresis revealed unusually low gamma globulin. No cryoglobulins were found. Gamma globulins were determined by the zinc II method of Kunkel (14), and averaged 14 units (normal range is 36 to 49 units).

The patient was started on prednisone 10 mg four times a day, and serial hemoglobins, reticulocytes, and electrophoretic patterns were obtained.

Values of hemoglobins, reticulocytes, and gamma globulin are summarized in Figure 2. Two bone marrows were obtained, one midway in the remission and one after complete remission. They demonstrated erythroid hyperplasia, very few eosinophils, and complete absence of plasma cells.

The patient was kept on a maintenance dose of 5 mg of prednisone and has continued in remission through December 1, 1960.

COMMENT

This is the first case to be reported in which an adult with erythrocytic hypoplasia has had three repeated remissions on steroid therapy.

The first remission occurred four weeks after the start of relatively small doses of prednisone (20 milligrams daily), and relapse occurred approximately 14 months later. No maintenance therapy was used. His second remission occurred approximately two weeks after the institution of prednisone (50 milligrams daily). He remained on maintenance therapy (5 milligrams daily) for three months, then discontinued it. Four months later he relapsed for the third time and began to remit within two weeks after starting prednisone (30 milligrams daily).

The first remission occurred four weeks after cobalt in small doses was discontinued. Similarly, in the second remission, the response occurred four weeks after crude liver, vitamin B-12, pyridoxine, and riboflavin were stopped. No other therapy but prednisone was used in achieving the third remission. Since all three remissions occurred while on steroids it seems clear that this is a therapeutic response.

A variety of therapies has been reported to be effective in erythrocytic aplasia including cobalt (15, 16), riboflavin (17), splenectomy (18),

adrenocortical steroids (19, 20), testosterone (21), and thymectomy. Spontaneous remission must be considered in some of these cases.

It is apparent that a disease which appears to respond to such varied therapies as drugs, vitamins, hormones, thymectomy, and splenectomy may have varied etiologies. This case suggests that prednisone should be given a trial in the course of therapy. Perhaps massive doses may be required in some cases.

This steroid may produce its effect by marrow stimulation or by interference with some undefined allergic or sensitivity reaction. The moderate eosinophilia present in the first marrow and two peripheral smears during relapse lends support to this concept. It is possible that eosinophilia found in other cases may point to adrenocortical steroids as the treatment of choice.

The absence of plasma cells was noted in retrospect after finding the reduced gamma globulin. Table I shows a summary of the pertinent bone marrow findings.

The data presented above demonstrate two cellular morphologic defects in the bone marrow of a patient with the clinical entity of erythrocytic aplasia. We may assume that the hypogammaglobulinemia is a reflection of the absent plasma cells. This relationship is clearly stated by Good (8). Plasma cells were absent from the marrow in the case of erythrocyte aplasia with hypogammaglobulinemia reported by Ramos (5).

It appears from the data in Figure 2 that prednisone had some common effect on the erythroid tissue and on the protein fractions. Gamma globulin rose as the reticulocyte response took place. The gamma globulin was secreted presumably by plasma cells. It did not reach normal levels even after full hematologic response. We may assume that there was some partial proliferation of plasma cells even though they were not evident on scanning the bone marrow slides.

Unusual relationships between erythrocyte hypoplasia, thymoma, and hypogammaglobulinemia have been recorded (5-8, 10). Thymoma has been associated with erythrocyte hypoplasia (6) and with hypogammaglobulinemia (10). Thymectomy did not affect the protein pattern in the case of Good and Varco (10), just as prednisone achieved only partial

TABLE I. Results of Bone Marrow Examinations

Bone Marrows	Relapse or Remission	Erythroid Activity	Plasma Cells
1. August, 1956	relapse	none	none
2. Nov. 1956	remission	full	none
3. Dec. 1956*	relapse	none	unknown
4. Feb. 1957*	remission	full	unknown
5. Oct. 1958	relapse	none	none
6. Nov. 1958	relapse	none	none
7. Dec. 1958	remission	full	none

* Information obtained from transmitted abstract.

improvement in the present case. The possibility of a common dysbiotropy to explain the varied pathologies mentioned above is referred to as "a failure of the reticulum with which may be associated neutropenia, eosinopenia, thymic tumor, reticulum cell proliferation, and deficiency of plasmacellular development from reticulum" (10).

It is difficult to avoid the conclusion that some basic cellular defect is present as the relationships of the apparently dissimilar abnormalities become apparent. Gamma globulin deficiency represents, then, a defect in cellular development rather than a problem in protein metabolism *per se*. It seems clear from the character of the related pathological conditions that the unifying cellular system involved is the hemopoietic system, and a more complete understanding of this system will clarify our present problem.

SUMMARY

A case of chronic erythrocytic hypoplasia with three remissions on steroids has been presented. In addition to the erythroid defect, the patient had no plasma cells, and a low gamma globulin. The gamma globulin increased as the erythroid tissue regenerated although plasma cells did not reappear.

A basic cellular defect to explain the simultaneous disturbance of both red cell and gamma globulin production is postulated.

SUMMARIO IN INTERLINGUA

Es describite un caso de hypoplasia erythrocytic e hypogammaglobulinemia sin apparente etiologia incontrate in un masculo de juveme etate. Iste paciente habeva tres separate

recidivas e tres remisiones inducidas per prednisona in le curso de un periodo de duo annos e medie. Ille eseva ancora in remission quattro annos e medie post le declaration initial del morbo. Le remission eseva mantenite per un medication de 5 milligrammas de prednisona per die.

Un serie de studios del medulla ossea efectuata in remission e in recidiva revelava absentia de plasmocytos. In le tertie recidiva, studios electrophoretic in serie eseva effectuata durante le curso therapeutic a prednisona. Durante que reticulocytos appareva e cresceva in numeros, le globulina gamma montava attingente un nivello levemente infra le norma.

Durante le recidiva, le nivelllos de erythropoietina eseva extrememente alte, e le metabolismo de ferro radioactive eseva extrememente basse.

Es opinate que iste caso exhibi duo defectos cellular fundamental—erythroide e plasmocytic—with resultante anemia e hypogammaglobulinemia. Iste combination de defectos reflecte possiblemente un anormalitate genetic de character plus fundamental.

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Human Heart Failure and Shock Treated by Means of a Mechanical Veno-arterial By-pass without Oxygenation

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WHEN CORONARY CIRCULATION is critically reduced cardiac contractile power declines (1-5). When the fall in myocardial contractility results in systemic hypotension, an associated decrease in coronary blood flow may occur and become an important factor in sustaining the hypotensive shock. Previous reports (5-7) described an effective method of interrupting such a vicious cycle in dogs put into shock and heart failure by pulmonary artery constriction. Elevating systemic blood pressure by pumping part of the venous blood (without oxygenation) into a systemic artery (V-A pumping), sharply increased coronary blood flow and resulted in functional recovery with reversal of experimental heart failure and shock without removing the disabling fixed overload (pulmonary artery constriction) used to induce these complications. In view of these experimental results, it seemed reasonable to explore the clinical usefulness of this technique in reversing shock associated with heart failure in patients. This report describes its application in a patient with shock and heart failure following acute myocardial infarction.

CASE REPORT

A 76-year-old woman was admitted to Alta Bates Hospital, Berkeley, California, on July 3, 1959, at 3:00 PM. One and one-half hours earlier she had felt sudden, severe chest pain radiating down the left arm, accompanied by weakness, sweating, and nausea. An hour later she was examined by her physician. Her skin was pale, cold, and moist; blood pressure was 90/70 mm Hg; the pulse was weak, the heart rate 60/minute and regular. The first heart sound was faint; no murmurs were heard.

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The lungs were clear. No abnormality was detected within the abdomen. No cyanosis or edema was observed. Morphine sulfate (10 mg) was administered, and the patient was sent by ambulance to the hospital with a diagnosis of shock following acute myocardial infarction.

Three years earlier, in 1956, the patient had been confined in the same hospital for the treatment of myocardial infarction. She had recovered and remained well until a few months prior to admission, when she had undergone several episodes of biliary colic with radiographic demonstration of gallstones.

At 3:00 PM the patient was admitted to the hospital still complaining of chest pain and extreme nausea. She was pale and sweating; her skin was cold and clammy. Her blood pressure was 90/60 mm Hg; pulse rate, 60/minute; respiratory rate, 16/minute; rectal temperature, 97 F. An electrocardiogram was consistent with a fresh posterior myocardial infarction superimposed upon residual changes from the old infarct. There was evidence of numerous multifocal ventricular premature beats. The patient was put into an oxygen tent and given 10 mg prochlorperazine intramuscularly.

At 4:00 PM the pulse became weak and rapid; blood pressure was unobtainable. The apical heart rate was 60/minute. The first heart sound was inaudible. Ephedrine, 50 mg, was given intramuscularly and the patient was placed in the Trendelenberg position.

At 6:30 PM the patient began to complain of air hunger and became very restless. Respirations were rapid and shallow. The skin was cold and pale. The blood pressure was 75/50 mm Hg; apical rate, 120; respiratory rate, 36/minute. The heart sounds were soft and distant. Diffuse bubbling rales and wheezes were heard throughout both lung fields. Acute pulmonary edema was evident. Digoxin, 0.8 mg intravenously and 0.8 mg intramuscularly, was given. At 7:00 PM, 10 mg of morphine sulfate and 0.2 g of quinidine sulfate were given. Because of the persistent shock and the onset of acute pulmonary edema, a trial of veno-arterial pumping was made beginning at 8:50 PM (5). The procedure was carried out in the patient's room because removal to the operating room was considered too hazardous. The left leg was packed in ice. The area about the upper left thigh and groin was prepared and draped aseptically, then infiltrated with 1% lidocaine. A five-inch incision was made over the femoral pulsation in the groin, and carried into the upper thigh. The subcutaneous tissue was divided and the femoral artery and vein identified.

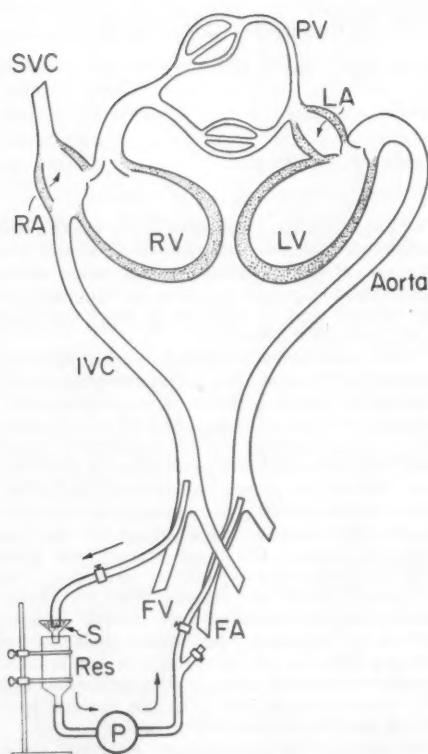


FIGURE 1. Circuit diagram of veno-arterial bypass. Venous blood drains by gravity to a reservoir (RES), through an "anti-foam" impregnated sponge (S). A sigma motor pump (P) returns blood to femoral artery (FA).

After the vein had been dissected, a longitudinal incision was made and a large plastic cannula was inserted into the vein cephalad for a distance of about four inches. The femoral artery was then identified and freed for a useful distance above and below, and bulldog clamps were applied to control bleeding. A longitudinal incision was made in the femoral artery, and a large plastic cannula was inserted for a distance of three inches, approximately to the bifurcation of the aorta.

Figure 1 is a schematic diagram of the pump circuit. Heparin (1 mg/kg) was given to prevent clotting. The femoral artery was clamped below the cannula at 9:10 PM. The apparatus was filled with a unit of cross-matched blood, and all air was removed from the tubing.

The veno-arterial bypass was started at 9:50 PM. Within a few minutes the systolic pressure increased to 115 mm Hg (Figures 2 and 3) and averaged about 90 mm Hg while pumping was in progress. The heart rate, which had been 100/min-

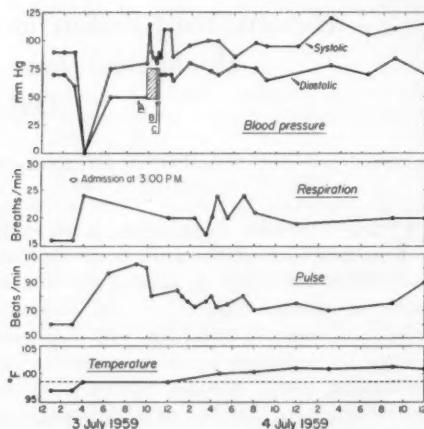


FIGURE 2. Graph of vital signs during the first 36 hours after myocardial infarction. The cross-hatched box represents the period of veno-arterial pumping. "A," the femoral artery was clamped; "B," the multifocal premature ventricular beats were no longer present; "C," pulmonary edema cleared.

ute prior to shunting, decreased progressively. During the shunting procedure the respiratory rate decreased, dyspnea gradually diminished, breathing became progressively less labored, and the patient became much more comfortable. The frequent multifocal ventricular premature beats observed prior

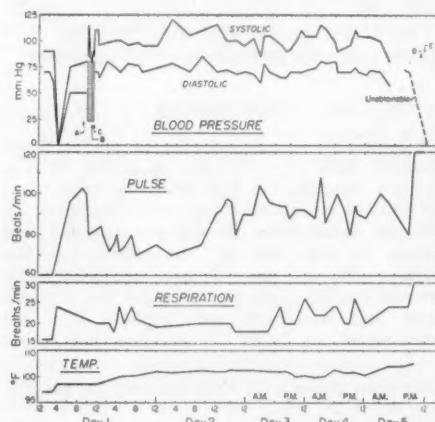


FIGURE 3. Graph of vital signs following an acute myocardial infarction with shock treated by means of veno-arterial bypass (cross-hatched box is the pumping period). "A," femoral artery clamped; "B," multifocal ventricular extrasystoles disappear; "C," pulmonary edema cleared; "D," blood transfusion; "E," l-norepinephrine infusion.

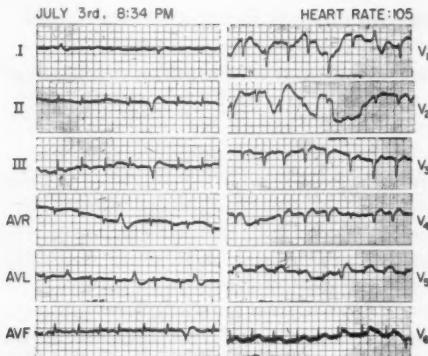


FIGURE 4. Electrocardiogram taken just prior to veno-arterial pumping procedure. S-T segments are elevated and Q waves are present in leads II, III, aVF, V₅-V₆. Note the frequent multifocal ventricular extrasystoles.

to pumping (Figure 4) were still present during the first 30 minutes of veno-arterial pumping (Figure 5) but disappeared (Figure 6) after 64 minutes. The patient became mentally alert during the procedure and frequently asked the score of a baseball game that was in progress.

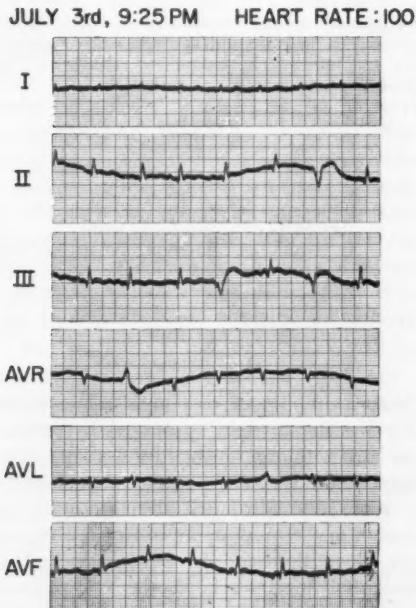


FIGURE 5. Electrocardiogram taken after 30 minutes of pumping. Ventricular extrasystoles are still present but appeared to be less frequent.

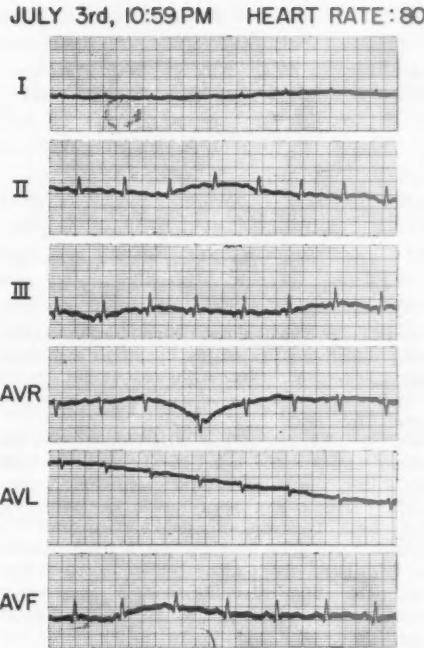


FIGURE 6. Electrocardiogram after 64 minutes of veno-arterial pumping. Ventricular extrasystoles are no longer present. Heart rate has decreased to 80 beats per minute.

After 70 minutes, the by-pass was discontinued; the cannulae were removed, the vessels repaired, and the wound was closed. Left pedal pulsations were good. The blood pressure was 110/70 mm Hg; the heart rate, 80 per minute. The lung fields were clear to auscultation except for a few wheezes at the bases. Pulmonary edema had cleared completely. The skin and extremities were warm. Pallor disappeared and sweating ceased. After almost ten hours of shock and four hours of pulmonary edema, veno-arterial shunting for one hour and ten minutes was followed by disappearance of all signs and symptoms of shock and heart failure (Figure 2).

During the next 12 hours the patient continued to improve, remaining normotensive (Figures 2 and 3) and free of pain. The lungs were completely clear of rales, and there was no evidence of heart failure. The rectal temperature rose after completion of the procedure to 100 F. The administration of heparin and digoxin, 0.25 mg daily, was continued.

The patient remained free of heart failure and shock during the next four days (Figure 3). On the evening of the third hospital day, a pericardial friction rub was heard for the first time. There was intermittent, mild chest pain, easily controlled with 10 mg of morphine. On the fourth hospital day, diarrhea developed, without abdominal pain or

TABLE 1. Significant Laboratory Data

Date	Hematocrit (%)	Hemoglobin (g/100 ml)	White Blood Cells (mm^3)	Clotting Time* (minutes)
July 3, 1959 (admission)	41	13.0	9,400	
July 4	40	12.9	14,800	41
July 5				14
July 6				14
July 7			19,500	16
July 8	29	9.2		20

* Lee-White.

tenderness. A hematoma was found to be accumulating under the site of the operation and small amounts of serosanguineous fluid drained from the wound; the quantity of heparin administered was sharply decreased.

On the morning of the fifth hospital day the patient sat up and dangled her legs over the side of the bed. She felt well, and except for the persistent diarrhea and temperature elevation, was doing well. The electrocardiogram remained unchanged. Antibiotic therapy was started. As the day progressed the patient became somewhat lethargic. Five hundred milliliters of 5% dextrose in saline solution with an additional 15 mEq of potassium chloride were administered intravenously, and the patient improved. At 10:00 PM her condition suddenly deteriorated. She became semi-comatose and dyspneic. The respiratory rate was 24/minute; pulse rate, 96/minute; blood pressure, 80/60 mm Hg. The heart sounds were distant. The lung fields were clear, and no peripheral edema was observed. Deterioration continued during the morning of the sixth hospital day. By 8:30 AM, the patient was stuporous and talked irrationally. Blood pressure became unobtainable (Figure 3). Radial pulsation was intermittently barely palpable. Heart sounds continued to be distant, and atrial fibrillation with a ventricular rate of 90/minute was now present. There were scattered moist rales in both lung fields, especially over the right base. Because the hemoglobin level fell to 9.2 g/100 ml, and the packed red cell volume to 29%, blood transfusion was begun. The blood pressure responded neither to blood transfusion nor to l-norepinephrine supplied by intravenous drip. The patient died a few hours later.

Laboratory Data: Serum transaminase 316 units/ml/minute on admission.

Following veno-arterial pumping, serum bilirubin was 0.1 mg/100 ml direct, 0.3 mg/100 ml indirect. No methemalbumin was found in the serum. Other pertinent laboratory data are listed in Table 1.

Post-mortem Examination: A complete post-mortem examination was made. The significant findings were those of the heart and femoral vessels.

The pericardial sac contained an old fibrinous exudate on the posterior aspect of the left ven-

tricle, and a very fine, fresh, fibrinous exudate on the anterior surface of the left ventricle which extended inferiorly to the apex. The heart was markedly dilated and flabby. An area of old fibrosis, 2 to 3 cm in diameter, was present in the myocardium on the posterior aspect of the left ventricle near the base of the heart. Mottled, rather diffuse areas of myocardial degeneration involved the posterior, septal, and anteroseptal portions of the left ventricle, with the posterior apparently more intensively involved than the anterior. The coronary vessels were markedly sclerotic. The right coronary artery was completely occluded 4 or 5 cm from its origin by a thrombus 2 or 3 cm in length. The clot was pale, organized, and appeared to be days old. The left anterior descending branch, at a point about 5 cm from its origin, contained a fresh thrombus approximately 2 cm long; the clot appeared to be hours old and was easily expressed from the lumen. The circumflex artery, although markedly sclerotic, was not occluded.

The left femoral vessels were intact and widely patent. Ecchymoses surrounded both vessels.

Pathologist's Diagnosis:

- I. Generalized arteriosclerosis with:
 - A. Coronary sclerosis and occlusion, old, recent (days old), and fresh, with:
 - 1. Myocardial infarction, old, recent (days old);
 - 2. Aortic sclerosis.
 - B. Bronchopneumonia.

DISCUSSION

Wiggers (8) found that myocardial contractility was impaired by prolonged hypotension associated with experimental hemorrhagic shock. Opdyke and Foreman (9) confirmed these observations and attributed the myocardial depression to the pressure dependent fall in coronary blood flow and its associated effect on myocardial metabolism. Boyer (10) directed attention to this mechanism as a possible factor sustaining shock following myocardial infarction. Various methods of combating this form of shock have been explored (11-13).

There seems little doubt that this patient's dramatic emergence from almost ten hours of shock (established on the basis of clinical findings including hypotension) and four hours of pulmonary edema was related to the veno-arterial pumping procedure. Moreover, her freedom from heart failure and shock, with cardiovascular system well stabilized for four days after the procedure, indicates that short periods of support may yield prolonged benefits. Prolonged improvement in cardiac function (following brief periods of veno-arterial pumping) sustained after the pumping was discontinued, was also observed in our animal experiments, where it was termed the "accommodation phenomenon" (5).

The usual treatment of non-hemorrhagic shock commonly employs one or another of the pressor amines, and it is in comparison with this procedure that the possible advantages of veno-arterial by-pass must be considered. In comparable experiments using l-norepinephrine to treat experimental heart failure and shock induced by pulmonary artery constriction, Fowler, Duchesne, and Franch (14) did not observe an accommodation phenomenon; instead, there was very transient initial improvement followed by a progressive decline in cardiac performance after successive interrupted periods of l-norepinephrine infusion. Moreover, the fact that sustained experimental heart failure is produced in normal dogs when l-norepinephrine is first infused, and then discontinued (15) is strong evidence for the ultimately deleterious effects of this agent on the myocardium. Further advantages of veno-arterial by-pass over pressor amine therapy are considered on the following physiological grounds: [a] The pumping reduces the volume of blood that the depressed myocardium is obliged to pump, by the amount that is by-passed; [b] Coronary circulation is improved without concomitantly reducing cerebral (16), renal (17), or hepatic (18) blood flow; [c] Increased myocardial metabolic requirements (14) and the frequently occurring cardiac arrhythmias (19) that accompany the use of pressor amines are absent; [d] The occurrence of an accommodation phenomenon (5), which demonstrates that the critically stressed heart has a capacity to adjust to and sustain previously disabling loads

after it has been assisted by veno-arterial pumping.

Evaluation of the role of the by-pass in this patient's improvement must include consideration of the drugs administered and of the complications that developed.

The digitalis given three and one-half hours prior to shunting could conceivably have contributed to the improvement in cardiac function. But the full effect of the digoxin, which was parenterally administered, should have obtained before the by-pass was started. There was clearly no beneficial effect on shock or pulmonary edema before pumping.

The 0.2 gram of quinidine given intramuscularly at 7:00 PM might have been sufficient to suppress the multifocal ventricular extrasystoles. The extrasystoles did not disappear, however, until 64 minutes after pumping was begun (Figure 5); this was four hours after the quinidine had been given. The dose of quinidine was minimal, and its effect would almost certainly have been largely dissipated after four hours, provided it was absorbed.

It is possible that both digoxin and quinidine were poorly absorbed because tissue circulation was inadequate during shock. As veno-arterial pumping improved circulation, these drugs could have been absorbed more efficiently and could then have contributed to the general improvement in cardiovascular status.

Although the drugs may have contributed to the over-all improvement, the observation remains that the patient emerged from an almost hopeless state only following the pumping procedure. After the procedure her condition stabilized and she seemed likely to recover. Her ultimate death on the sixth hospital day appeared to be independent of the successfully treated circulatory collapse that followed the second coronary occlusion.

The hemorrhagic complications that arose not only influenced her course, but probably contributed to the third myocardial infarction, which preceded her death by a few hours on the sixth hospital day. The appearance of the ecchymosis around the operative site led to discontinuation of effective anticoagulant therapy. The quantity of clotted blood found at autopsy to have infiltrated the area around the vessels appeared sufficient to account for the decrease in the hematocrit level from 41% the

day after the procedure to 29% on the morning of the sixth hospital day. The extent of blood loss was not appreciated until late because the slowly leaking blood dissected deeply into the tissues and bulged little under the skin surface. Earlier recognition of the blood loss and resuturing of the leaking vessels might have prevented the fatal episode.

The severe, persistent diarrhea from some unknown cause undoubtedly affected hydration still further. Fluid and electrolyte replacement, held to conservative levels in an effort to prevent recurrence of heart failure through overhydration, was perhaps inadequate to compensate for the diarrhetic state. Thus, blood loss, fluid loss, and lack of effective anticoagulation probably combined to set the stage for the third and fatal coronary occlusion.

The temperature elevation was most likely due to the extensive necrosis of the myocardium, since it became apparent as soon as the patient emerged from shock. The bronchopneumonia was undoubtedly a terminal event.

While a single and not unqualified success with the veno-arterial by-pass procedure is not a significant test, sufficient theoretical and experimental grounds exist to justify a systematic clinical trial of this technique in the treatment of shock with heart failure.

SUMMARY

The use of a veno-arterial by-pass procedure on a patient in shock and heart failure following an acute myocardial infarction is described. The potential value of this procedure in the treatment of shock is considered and its advantages over pressor amine therapy are discussed.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Es describite le uso de un shunt veno-arterial effectuate in un paciente in choc e disfallimento cardiac post acute infarcimento myocardial. Le valor potential de iste metodo in le tractamento de choc es discutite insimul con su avantages in comparation con un therapia a aminas pressori.

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Use of an Air Force Antigravity Suit in a Case of Severe Postural Hypotension

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THE PROBLEM OF ORTHOSTATIC HYPOTENSION can be a very perplexing one. This problem may be apparent to the physician in his attempts at treatment, and to the patient by the degree of disability which may be sustained despite intensive therapy. The striking postural fall in blood pressure is stated by Sieker, Burnum, Hickam, and Penrod (1) as primarily occurring from failure of the peripheral arterioles to constrict and maintain resistance when the patient stands. Associated with this is a decrease in the cardiac output and impairment of venomotor ability giving a decreased venous cardiac return. Wright (2) states that the venous return is governed by the contractions of the skeletal muscles in squeezing blood towards the heart; inspiration, by increasing negative pressure in the thoracic cavity and increasing the intra-abdominal pressure; the slightly positive capillary pressure, which propels blood towards the heart; and gravity, which both aids and hinders this return.

In addition to treatment of orthostatic hypotension by sympathomimetic drugs and elastic bandages, a new application of an old concept has been gaining attention (1, 3-6). This is the

use of some type of counter-pressure garment. We have recently had good results in the treatment of such a case.

CASE REPORT

A 67-year-old British housewife had been in good health until 1958, when she sought medical help because of urinary incontinence. The finding of incontinence with associated bladder retention, in addition to a history of the absence of sweating for many years, led those who saw her to consider a diagnosis of multiple sclerosis. The patient did fairly well with her initial complaint until April 1959, when she began to develop additional symptoms upon standing. These consisted of blurred vision and weakness, progressing to syncope. They increased in frequency until she was unable to stand without lapsing into unconsciousness. In November 1959, when she was admitted to St. Michaels Hospital, Braintree, Essex, England, her blood pressure was 140/90 millimeters of mercury, supine. Upon her sitting, the blood pressure dropped to 110/80 millimeters of mercury, and upon her standing for three minutes, the blood pressure was unrecordable. After six to eight minutes in the supine position, her blood pressure gradually returned to its original level of 140/90 millimeters of mercury and she regained consciousness. The pulse appeared to remain at 80 throughout the episode, although it was not obtainable while the patient was standing. A minor ataxia of the lower extremities, more prominent on the right, was noted also. She was incontinent at times, particularly regarding urge and stress, but no longer carried residual urine in the bladder. Epinephrine raised the blood pressure from a sitting level of 85/70 to 140/115 millimeters of mercury. The cold pressor test was negative, and neither arterial occlusion of the thighs, nor atropine 0.15 milligram intramuscularly, altered the course of

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FIGURE 1. United States Air Force antigravity suit, type G-3A. The outer covering has been opened to show the inflatable bladder system.

the syncope. It was believed that a central nervous system lesion existed, resulting in loss of sympathetic function.

In an attempt at rehabilitation, a G-3A chap type standard Air Force antigravity suit of the type currently in use by jet pilots in the United States Air Force was obtained (Figure 1). Although the fit was somewhat difficult because of the woman's anatomical makeup, inflation of 20 millimeters of mercury enabled the patient to stand for four minutes and take a few steps without recurrence of her syncopal symptoms (Figure 2). Subsequent measurements with the legs encased in elastic bandages and a suit inflation of 35 millimeters of mercury disclosed a blood pressure drop of 150/100 to 90/60 millimeters of mercury when the patient stood. The pulse remained constant, and she was free of symptoms while standing a total of ten minutes.

The patient has continued to wear the suit and is now ambulatory with assistance.

COMMENT

The application of the pressure suit principle is an old one. Crile (7) describes a rubber inflatable suit which "constituted an artificial peripheral resistance." This was devised for use in cases of shock following surgical procedures,

but as transfusion refinements came into vogue the suit lost favor only to become prominent again in the era of high speed flying.

The type of suit used in our case consisted of interconnected abdominal, thigh, and calf bladders in an adjustable chap type garment which permitted close fitting. As used in jet aircraft, the suit is connected into a metering device that allows inflation or deflation as gravitational forces are applied to the aircraft. The effect of this suit is to prevent the pooling of blood in the lower extremities and splanchnic areas, thus eliminating "blackout" as the pilot is subjected to gravitational forces.

The largest series reported on the use of pressure garments in cases of postural hypotension was that of Sieker et al. in 1956 (1). These investigators used a neoprene impregnated double walled nylon sheet encasing the abdomen and lower extremities of ten patients with severe postural hypotension. By inflating this device to a pressure of 25 to 30 millimeters of mercury, they found that on a tilt table they could maintain blood pressures of around 40



FIGURE 2. Patient standing. The suit has been inflated to a pressure of 20 millimeters of mercury.

millimeters of mercury higher than those encountered without the suit. They were also able to increase cardiac output in these patients, and believed the suit acted by supporting peripheral resistance and promoting return of venous blood to the heart.

The greatest application of the counter-pressure devices appears to be in the field of surgery, particularly in areas where surgical procedures are best carried out with the patient in the sitting position. Freuchen (3), a neurosurgeon, used a Danish Air Force antigravity suit in operating upon 14 patients. These patients were all in the sitting position, and Freuchen found it easier to maintain constant values for blood pressure and pulse with the suit inflated to 25 millimeters of mercury than by using leg elastic bandages alone.

Other applications of the counter-pressure principle were by Gardner and Dohn (4), who successfully used a suit inflated to 10 millimeters of mercury in rehabilitation of a diabetic patient with severe orthostatic hypotension, and by Gardner, Taylor, and Dohn (5), who used a suit as a life-saving measure in a case of placenta percreta, in which hemorrhage was not controlled with 55 transfusions and packing alone.

SUMMARY

A case of severe orthostatic hypotension has been reported in which the patient was dramatically helped by application of an Air Force antigravity suit.

ACKNOWLEDGMENT

The author wishes to acknowledge the assistance given by J. H. Ross, M.D., M.R.C.P., and John Blagdon, M.D., in the preparation of the material for this paper.

SUMMARIO IN INTERLINGUA

Es presentate un caso de hypotension postural satis sever pro confinar le paciente a su lecto. Le hypotension esseva refractori a therapias drogal sed esseva alleviate per le uso de un costume anti gravitate del statounitese Fortia Aeree, del typo currentemente usate per pilotas de jet.

Le paciente esseva un menagera britannic de 67 annos de etate qui disveloppava incontinentia urinari, retention vesical, ataxia del extremitates inferior, e incapacitate de sudar.

Le tension de sanguine del paciente in decubito dorsal esseva 140/90 mm de Hg. In position sedente, le tension declinava a 110/80 mm de Hg. Post que le paciente habeva essite in position stante durante tres minutus, le tension de sanguine esseva non-registrabile. Le frequentia del pulso remaneva 80 usque illo cessava esser palpabile. Epinephrina augmentava le tension de sanguine in position sedente ab 85/70 ad 140/115 mm de Hg. Le test a frigido pressori esseva negativo. Atropina intramuscular in un dosage de 0,15 mg e occlusion arterial in le femore non produceva un stabilisation del tension de sanguine.

In le effortio de rehabilitar le paciente, un costume anti gravitate del statounitese Fortia Aeree, typo G-3A, esseva applicate e inflate a 20 mm de Hg. Le paciente esseva capace a tener se erecte durante quattro minutus e facer plure passos sin recurrentia de su syncope. Quando le pression in le costume esseva aumentata a 35 mm de Hg, durante que le gambas del paciente esseva enveloppate in un bandage elastic, le tension de sanguine declinava ab 150/100 ad 90/60 mm de Hg e se stabilisava. Le paciente esseva libere de symptomas. Illa esseva ambulatori, ben que non sin assistentia.

Es presentate un revista del currente applicationes del principio del costume a contrapression.

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REVIEW

Tissue Transplantation

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ALTHOUGH, WITH RARE EXCEPTIONS, transplantation of tissue between nonrelated individuals has yet to be successfully achieved, recent advances in knowledge of the mechanisms responsible for this lack of success have stimulated widespread interest and have made it apparent that in certain areas at least the problems to be overcome are not insurmountable. Any review of tissue transplantation should begin with a definition of the terms to be used. Although Gorer (1) has recently introduced better terminology, the older, more widespread usage will be employed here. The term *autograft* refers to tissue which is transplanted from one portion of an individual to another part of that same individual. The term *homograft* is applied to tissue transplanted from one individual to another individual of the same species. *Heterograft* refers to tissue transplanted between individuals of different species. For human identical twins or animals so closely inbred that for practical purposes they are identical twins, exchanged tissue represents an *isograft*. Since an individual does not reject his own tissue, nor that of an identical twin, such tissue when transplanted may be expected to survive as a functioning viable graft. With rare exceptions, grafts of the other types are rejected by reason of the immune response to the donor antigens, which is to be the subject of this review.

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TRANSPLANTATION IMMUNOLOGY

The foundation for what is known about the immunology of transplanted tissue rests upon observations of two kinds of tissue, tumors and normal skin. Knowledge of the problems of normal tissue transplantation actually had its origin in the study of tumor transplantation, but as Medawar (2) has pointed out, "nearly everyone who supposed he was using tissue transplantation to study tumors, was in fact using tumors to study transplantation." For the study of the problems associated with normal tissue transplantations, skin is ideal since tumors are immunologically less sensitive and can overcome weak immunologic reactions which might cause rejection of skin (3). Furthermore, skin is easily transplanted, it can be observed grossly, and it can be biopsied for histologic observation.

The mechanisms responsible for the rejection of transplanted skin represent a fundamental biologic problem common to many kinds of tissue such as kidney and spleen (4), adrenal (5), nucleated leukocytes (6), and other tissues. In the past the thesis was generally accepted that transplantation immunity is individual-specific and not tissue-specific in the same species. This statement suggested that any nucleated tissue of an individual was capable of sensitizing a recipient of the same species to any other nucleated tissue of the donor. In the light of recent evidence this statement must now be modified and certain exceptions can be made in isolated instances such as parathyroid tissue, and the ovaries of certain strains of rats. There appears to be a difference between poly-

mophonuclear leukocytes and lymphocytes in certain other rat strains. In addition, the antigenic dose and the route by which the antigen reaches the antibody-forming mechanism may represent functional antigenic differences in tissues whose blood supply is different (i.e., skin and kidney). Nevertheless, the fundamental biologic mechanism of graft rejection appears to be essentially similar for all tissues.

THE MECHANISM OF REJECTION

We may best understand this mechanism by first reviewing what takes place when skin homografts are exchanged between adult mice of different inbred strains. If skin is transplanted from A to C57 strain for the first time the skin becomes normally vascularized as does an autograft of the animal's own tissue. For four to five days it may appear quite viable and blanch on pressure. Within six to seven days, however, it becomes inflamed and edematous. Eventually it ulcerates, becomes necrotic, and is rejected. Finally, it is replaced by overgrowth of the host's epidermal cells. If, following the rejection of the first piece of skin, a second piece is grafted from the same donor, the rejection of the second homograft is accelerated and sloughing takes place several days sooner than in the first instance. This suggests that the host has been "immunized" by the first tissue homograft so that it now "recognizes" a second graft from the A strain mouse and rejects it with greater speed. If, following the rejection of a second piece of skin from A strain, a piece of skin from a C3H strain is placed, it will survive a normal period of time. The inference is clear, then, that the mouse has been immunized against an antigen which is specific for the A strain. Since it has already been pointed out that skin, kidney, spleen, and adrenal behave in the same fashion, we conclude that the immune response is "individual-specific" and not organ or tissue-specific. With the exceptions noted, much of the

work leading to these conclusions has been done by Medawar and reviewed by him (2), and more recently by him and Brent (3).

The development of "immunity" in the recipient animal suggests a parallel with the immunity developed following exposure to other foreign antigens such as bacteria. Such similarities do exist, but there are wide and important differences. A bacterial antigen is, of course, a *heterologous* antigen whereas we are concerned principally with *homologous* antigens in the form of skin homografts, that is, grafts of skin from one individual to another individual of the same species. The evidence is good, however, that the rejection of the skin graft is related to changes in the lymphopoietic system resulting from exposure to antigen from the homografted tissue. This may be described by studying the response of skin grafts placed upon rabbits' ears. The experiments of Scethorne (7) point out that a skin homograft causes a considerable increase in the weight of the regional lymph node draining the graft. This weight increase is not due to the operative procedure since it is greater in the homografted than in the autografted animals. The enlargement of the node is associated with an increase in "large lymphoid cells" with large pale nuclei, prominent basophilic nucleoli, and basophilic cytoplasm staining pink or red with pyronin. Such cells are usually regarded as antibody producers and "there is very good evidence that these cells if not identical with one another, at least belong to the same general family that produce antibodies against bacterial and other antigens" (7). Removal of the regional node draining the skin graft will result in some prolongation of graft survival (8). The evidence so far, then, suggests that antigenic material from the skin homograft reaches a regional lymph node and stimulates antibody-producing cells which then are responsible for the destruction of the

graft. Histologic sections of the graft itself shortly before gross evidence of necrosis is visible show infiltration with round cells and a later thrombosis of small vessels with capillary hemorrhages and tissue necrosis. Observations in the human using stereomicroscopy (9) have shown slowing of blood flow through the capillaries, agglutination, thromboses, and hemorrhages, in that order. A source of difficulty in comparing results from various laboratories is lack of the exact criterion used for rejection of a skin graft. Gross observation alone may be difficult and the use of stereomicroscopy time-consuming. Perhaps the most accurate method is biopsy of the tissue with histologic analysis and grading according to the degree of change. Recent studies in which serial biopsies were done in human skin autografts and homografts have clarified the sequential changes which precede and accompany the rejection of human skin grafts. The rejection of skin in conditions where marked histocompatibility exists between donor and recipient may be extremely slow. In these circumstances skin undergoes very gradual changes (so-called "creeping rejection"). These changes may be slow and the replacement of donor tissue by recipient epithelium so gradual as to lead to the erroneous impression that the donor tissue has survived permanently. The use of tattooing and presence of melanin in the grafted tissue to indicate survival of the graft has not proved to be a reliable index of survival since such pigment may persist in the host following rejection of the graft. One accurate measure of graft survival, however, is the persistence of the distinctive sex marker on epidermal cells of human female skin. Small chromatin patches at the periphery of the nuclei of the cells are characteristic of the female skin cell and persistence of such chromatin in epidermal cells grafted to a male is a reliable indication of survival of the original graft.

ANTIGENIC DIFFERENCE: ROLE IN ANTIBODY FORMATION

Of fundamental importance to the biologic problem of grafting in general is the question of how the skin graft antigen stimulates antibody production. The admirable work of Gorer and Snell (1, 10) has shown that differences in the genetically determined structure of tissues will cause rejection of transplanted skin. These so-called "histocompatibility genes" reside in the chromosomes of all nucleated tissue. There appears to be no one transplantation antigen capable of causing rejection, but a number and variety of antigenic properties, some strong and others so feeble as to allow a skin graft to survive for more than 100 days (11). Successful transplantation depends upon the presence in the recipient of all dominant genes also present in the donor. When two individuals develop from a single fertilized ovum as in monozygotic or identical twins, this latter condition is met and skin and kidney homografts may survive indefinitely when transplanted between them (12). In a sense the monozygotic twins are the same individual. Their tissues bear the same antigenic "self-marker." When transplanted tissues with different histocompatibility genes, i.e., those marked as "non-self" (13) are transplanted, they are "recognized" as being foreign. Antibodies are formed against them and they are rejected. The fact that varying degrees of antigenic difference may exist is important, because it accounts for varying survival of tissues transplanted, and also for the ease with which tolerance may be produced to such tissues. Table 1 from Billingham and Sparrow (14) shows the median survival times of skin homografts exchanged between adult mice of different inbred strains. It is apparent that survival time between different strains may vary by a twofold factor depending upon the degree of histocompatibility. Peer (15) has shown that skin transplanted between

TABLE 1. Median Survival Times of Skin Homografts Exchanged between Adult Mice of Different Inbred Strains

Strain Combination	m.s.t. \pm Standard Error (days)	Strain Combination	m.s.t. \pm Standard Error (days)
A CBA	11.0 \pm 0.3	A 057	7
CBA A	10.2 \pm 0.3	C57 A	8
A AU	9.0 \pm 0.3	CBA AU	9
AU A	9.1 \pm 0.4	CBA C3H	13
C3H A	10 \pm	C3H CBA	15
A C3H			

mother and son may survive for as long as 253 days.

This has not been the case invariably, however, and in our work homografts between parent and child more frequently than not have normal "rejection times." Rogers' studies show that homografts transplanted in control conditions in nonrelated human volunteers survive for only seven to nine days, while skin homografts transplanted in dizygotic human twins may survive for periods of 19 to 20 days (16). It has been suggested that fetal skin when transplanted may survive for longer periods of time because of lack of full development of the antigenic difference (17, 18). This result, however, has not been confirmed by other observers (19). Even sex differences between donor and recipient may determine failure or survival of a skin graft. Skin grafts from pure bred mice will survive when transplanted to the F_1 hybrid* if the graft is made from female to female, or male to male. However, grafts are rejected if they are made from male to female, suggesting that the male which carries the Y chromosome, not present in the female, has a Y-linked gene which will cause graft failure (20). This particular antigenic difference is

so specific that it is possible to produce tolerance to transplanted skin for the male factor alone, even when it cannot be produced for the strain (21). Thus it can be seen that a multitude of factors determines survival or rejection of transplanted skin and that this is not an all-or-none phenomenon but a phenomenon which varies widely in degree. As to the nature of the transplantation antigen itself we have little conclusive evidence. It was suggested some time ago by Billingham, Brent, and Medawar (22) that transplantation immunity could be produced by a cell-free fraction which had some of the chemical characteristics of desoxyribonucleic acid. More recent evidence suggests that this is not the acid itself but perhaps a desoxyribonucleic acid-protein-mucopolysaccharide complex much like the blood group antigens. Certainly it appears to reside in nuclear fragments. Damage to the nuclei, or to the nucleated cells as in the preparation of cell-free antigenic material, or even in the handling of white blood cells may result in loss of the individual specificity. In these circumstances the antigens become weaker and are strain-specific, or species-specific, rather than individual-specific (23).

We have mentioned previously that lymphatic connection and vascularization (24, 25) appear to be necessary for the antigen to reach the antibody-forming sites. However, recent work suggests this need not be a permanent anatomic connection since skin grafts placed and turned daily on their bed so as to disrupt anatomic con-

* If two mice A and B are mated, the offspring will contain the histocompatibility genes of both parents. In addition, it will contain a third gene, AB, which is not common to either parent. Because it contains A and B, the F_1 hybrid offspring will accept grafts from both parent A and B, but the parents will reject grafts from the offspring because of the new antigen AB not present in either parent.

tinuity may still result in transplantation immunity after a period of four days (26).

The problem of how the "antibody" to transplanted tissue arises and its exact role in the rejection of the graft has been widely investigated. For an excellent resumé the reader is referred to the review of Brent et al. (3).

CELL-BOUND VERSUS CIRCULATING ANTIBODY

The bulk of evidence at the present time favors the thesis that rejection of homografts occurs via the action of immune bodies, cellular and noncellular, arriving first by way of the vasculature supplying the graft. The difference between cellular or cell-bound antibody and noncellular antibody may simply be a quantitative one with the latter representing the peak immune response.

The fundamental work of Algire, Weaver, and Prehn (27) suggests that it is the sensitized lymphocyte of the recipient which is primarily responsible for graft rejection. In their work, donor tissue placed in a small chamber (millipore membrane) whose pore size was large enough to admit the constituents of circulating plasma, but not cells, was able to survive indefinitely, whereas it died when recipient lymphocytes were added to the chamber. It seems possible that such sensitized lymphoid cells arising in the lymph node as a result of antigenic stimulation bear on or in them specific antibody. In some fashion they may be attracted to the graft as they circulate in the plasma (28). Our own work (29) suggests that this is indeed the case, and further suggests that it is the sensitized recipient lymphocyte that is destroyed by contact with the antigen. The liberation of "antibody" or simply the products of cell destruction may result in rejection of the graft. The phenomenon of localization of host round cells and their destruction at the site of the graft has been noted by other observers (29).

Except in mice, circulating antibodies have not been conclusively demonstrated in the serum as a result of the development of immunity to skin homografts. In mice, it is probable that the transplantation antigen and those antigens responsible for the development of hemagglutinins following rejection of skin by mice are different substances with the same genetic and immunological specificity and therefore with the same determinant groups. Although this is the generally held opinion, some observers have claimed to demonstrate circulating antibodies in the serum by means of the transfer of homograft immunity with sera of animals who have rejected one or more skin homografts (24).

TEMPORAL ASPECTS OF REJECTION

The time of onset of transplantation immunity to skin grafts varies somewhat with the experimental animal used and the method of transplantation. Billingham and his co-workers have recently studied these factors (30). They find that in guinea pigs, measurable transplantation immunity occurs within two to three days after the first exposure to foreign homologous cells. Histologic assay of second skin grafts placed as long as 240 days after the first shows definite evidence of residual immunity even after this length of time. Second set homografts applied two to three weeks after a first graft are temporarily accepted and then rejected in an accelerated fashion. If, however, a second graft is placed eight to ten days after the first one, the second graft does not become vascularized and eventually dries up. This type of response is known as a "white graft" reaction. It is suggested that the "white graft" response occurs because it is placed at the time of a peak titer of "circulating antigrant antibodies" which never allow it to become vascularized. Second grafts placed more than two weeks after the first are not confronted with circulating antibodies but

restimulate already sensitized lymphoid tissue which results in an accelerated rejection. These observations have been made in both man (31) and in rabbits (24).

TOLERANCE TO GRAFTS

It has already been pointed out that tolerance for skin homografts depends in part upon the degree of histocompatibility between donor and recipient. Tolerance, however, may be induced or "acquired" by one of several techniques which have received considerable study in recent years. Naturally-occurring tolerance is related to the closeness of fit of the histocompatibility genes and is typified by prolonged tolerance for skin homograft between dizygotic twins and by the acceptance by F_1 hybrid mice of homografts transplanted to them from members of either of their parental inbred strains. "Acquired tolerance" is defined by Billingham et al. (32) as "an induced state of specific non-reactivity towards a substance that is normally antigenic." Billingham and his co-workers noted that skin grafts might be successfully accepted by dizygotic cattle twins, even when they are of different sexes and of obviously different genotypes. They ascribed this to the prenatal exchange of cells circulating in the fetal blood vessels and felt that this exchange of cells between two genetically different individuals at an early stage of the development of their antibody-forming system produced a long-lasting state of tolerance for any other tissue from these individuals (33). In other terminology such acquired tolerance might be explained by the fact that the antibody-forming system of one individual exposed to foreign cells at a time when it was too immature to distinguish "self" from "non-self" included the foreign cells in the "self" category. Since transplantation immunity is an individual rather than a tissue-specific problem, such tolerance would hold for the other tissues including skin homografts. Billingham and his collaborators were able to produce "ac-

tively acquired tolerance" in the mouse by injecting the mouse embryo *in utero* with living tissue antigens from a homologous strain. Embryos so injected would accept, as adult animals, skin from the strain whose cells had been used to inject them before birth (6). Since the initial observations of Billingham and his co-workers, tolerance for skin homografts has been produced in this fashion for a variety of species. In some species, such as the rat, injection of the newborn animal rather than the embryo will also produce tolerance.

The prolongation of the life of skin homografts may be brought about by the administration of cortisone or by X irradiation to the recipient; Billingham (32) does not believe this should be described as tolerance since it is not specific for an individual homograft strain. For our purposes, however, it seems simpler to class any technique for the prolongation of skin homografts as a form of "acquired tolerance." In this view a third form of acquired tolerance may be produced by the use of the whole body lethal irradiation (34). Since such doses of X irradiation destroy the hematopoietic system, as well as the lymphopoietic system where antibodies are presumed to be formed, survival can be accomplished only by the transplantation of bone marrow from the donor animal. This transplanted marrow reseeds the marrow spaces of the irradiated animal and produces formed elements of the blood which have the antigenic characteristics of the donor animal. Since the recipient now contains circulating cells of donor origin, it will also tolerate skin from the same donor. Here the "acquired tolerance" is "radiation-induced tolerance." It is brought about by destruction of the antibody-forming system so that donor bone marrow and skin grafts cannot be rejected. The use of this technique permits successful skin transplantation, even from a heterologous species, and rat skin has been successfully transplanted to mice following irradiation of recipient

and injection of rat bone marrow. Suppression of antibody-forming potential by anti-metabolites has also been shown to prolong the life of skin grafts (35). Another form of "acquired tolerance" to skin may occur following severe chronic illness and trauma. Prolongation of the life of skin homografts has been observed in chronic uremic patients (36) and severe burns (37). In both these situations it is assumed that severe illness and disability impair the immune response to grafted tissue.

Woodruff believes that skin homografts may "adapt" after a period of survival in a partially tolerant animal. Skin homografts which survive more than three months may survive indefinitely, even after the tolerance has been abolished, as evidenced by the rejection of a second skin homograft from the same donor. Woodruff believes that in these circumstances the first graft has adapted in such fashion that it can now survive in an animal no longer tolerant to tissue from the original donor (38).

There is some evidence that tolerance to skin homografts from animals whose tissues have not been used to inject the recipient animal may be produced by use of pooled cells from a number of donors (39, 40). Prolongation of the survival time of skin homografts may also be produced by prior intravenous injection of dissociated epidermal cells from the prospective donor (14). This effect has been described by the authors as "enhancement" rather than tolerance. It is thought that possibly this enhancement of the life of the skin homograft might be related to the effect of the intravenous epidermal cells in temporarily suppressing antibody formation against the antigenic configuration of the donor. A similar suppressive effect by large doses of antigen has been suggested by Zotikov (41) who found that extremely large skin homografts survived much longer periods of time than did smaller ones.

GRAFT VERSUS HOST REACTION

The production of tolerance by the injection of living cells has given rise to an unforeseen and disturbing consequence. The use of spleen cells, or even peripheral leukocytes, for this purpose entails the use of tissue which in itself has an antibody-forming potential. If such cells are tolerated by the host and multiply in him, it seems not unreasonable to postulate that the host tissue as a foreign antigen stimulates an immune response in these immunologically competent cells which are now being tolerated. This in fact appears to be the case. Mice which have been made tolerant to tissue of a foreign strain by the intraembryonic injection of spleen cells from this strain may develop a syndrome characterized by lack of growth, dermatitis, diarrhea, and early death ("runt disease"). Similarly, adult animals that have been irradiated and made to tolerate bone marrow may develop a similar syndrome, thought to be the result of immunity developed by immunologically competent donor cells against their host. In many instances this graft versus host reaction appears to be the result of suppression (or destruction) of the host's own immune processes by which bacterial flora are normally kept in check.

TRANSPLANTATION OF OTHER TISSUES

The preceding discussion of transplantation of skin applies in general to transplantation of other tissues with a few specific exceptions. Bone grafts and blood vessel grafts do not survive as viable donor tissue. Their function is largely to serve as supporting structures into and over which host tissue may grow, or as a bridge between portions of host tissue. Transplantation of the cornea is successful, apparently because it is not vascularized in its normal position. Transplantations of cornea to sites on the chest wall, for example, do become vascu-

larized and destroyed, as is any homograft. Apparently because of its lack of lymphatic supply the brain may act as a privileged site for homografts which survive longer when transplanted to the brain than to subcutaneous sites. There is some evidence that this is also true of the testicle. The cheek pouch of the hamster is also a privileged site for homografts. The particular structure of the connective tissue of the cheek pouch apparently protects grafts either by preventing graft antigen from reaching reactive sites or by preventing immune bodies in the host from destroying the graft. The use of artificial membranes, such as the millipore membrane, to protect nonvascularized grafts, has been investigated, using adrenal, thyroid, and ovarian tissue. There is some evidence that adrenalectomized rats may survive with adrenal homografts protected by such millipore chambers. Small fragments of thyroid homografts have been shown to take up radioactive iodine weeks and months after transplantation in millipore chambers. Depression of follicle-stimulating hormone, presumably by-products of slices of ovarian tissue transplanted as homografts in millipore chambers, has been reported in rats. The use of this technique, however, has been generally plagued with the problem of inability to maintain adequate nutrition and oxygenation of the transplanted tissue through the millipore barrier.

It has been suggested that fetal tissue, or neonatal tissue, is less antigenic than adult tissue (a fact which has been strongly questioned by several workers). For this reason and because of its growth potential, transplantation of fetal thyroid and parathyroid in humans has been attempted by a number of workers. The consensus at the present time, however, is that there is no evidence that such grafts have survived as functioning tissue for more than short periods in the human (42).

KIDNEY TRANSPLANTATION

Of the primarily vascularized grafts the kidney has been most extensively studied.

A kidney transplanted from one individual to another individual of the same species either human or animal fails to survive. There are, however, some differences which suggest that the transplantation of the kidney from one individual to another at least may take advantage of factors which do not affect the survival of other transplanted tissues. First of all, the transplanted kidney represents a large antigenic dosage; large doses of antigen are known to produce tolerance more effectively than smaller dosages, as has been discussed above. Antigen shed from a transplanted kidney reaches the recipient by the intravenous route, i.e., the renal vein. The intravenous administration of antigen is preferable to subcutaneous or intracutaneous administration in the production of tolerance (6). The kidney is an actively metabolizing, viable tissue, and cell viability is one of the prerequisites for the production of tolerance (6). From the point of view of the potential human donor the kidney has a special place also. The normal donor has two kidneys and can live perfectly well with one. On the other hand the potential recipient needs only one kidney to live a normal life span. Furthermore, recipients of transplanted kidneys should be chronically uremic, and it has been pointed out such patients tolerate grafts of skin better than normal healthy individuals (36). One of the major problems in the transplantation of viable tissue has been the possibility that once successfully transplanted, the donor tissue may form antibodies against the host (graft versus host reaction). The suggestion has been made by two observers (4, 43) that transplanted kidneys in dogs may perhaps form antibodies against the host. Careful histologic examination of transplanted kidneys which have been rejected by human

patients, however, reveals no evidence that this is so in the human. Furthermore, the careful experimental work of Porter and Calne has shown that the lymphocytes occurring in the rejected kidney are solely of donor origin (44). The experiments of Wheeler and Corson (45) with the transplantation of kidney slices between parents and F₁ hybrids have shown that the transplantation reaction occurs only when the recipient is capable of the immunologic response.

First reports on renal homografts in animals were published by Ullman (46). In 1908 Alexis Carrel reported experiments in which auto-transplants as well as homo-transplants were performed in dogs and cats (47). These studies were extended by Williamson (48,49). Both Carrel and Williamson failed to achieve success, and both commented on the interstitial plasma cell infiltration accompanying rejection. However, it was not until the work of Simonsen in Denmark and Dempster in England (43, 50) that the problems of renal homotransplantation in dogs underwent thorough study, and much of our fundamental knowledge on this aspect of the transplantation problems stems from their observations. Neither of these authors achieved more than transient prolongation of kidney graft survival with any of their methods, but their observations on technique in relation to kidney grafting to the general problem of tissue transplantation and the histology and physiology of the rejecting transplant were important contributions.

The author's personal experience with transplantation of kidney in the human includes 26 patients in whom kidneys were transplanted from nonrelated individuals without attempts at modification of the immune response, and seven patients in whom irradiation was given in an attempt to modify the reaction. In our clinic, kidneys have been transplanted between 15 sets of identical twins, and elsewhere in

the United States three other kidneys have been transplanted between identical twins. It should be emphasized at this point that kidney transplantation in the human is at present possible only in an institution which is equipped by experience to deal with the problems of critically ill, chronic uremic patients, since the management of such patients prior to and following the transplantation requires skill and experience in the treatment of chronic renal failure with its many and varied complications. The role of the artificial kidney in treating such patients has been an important one (51).

The first reported case of a kidney homograft in the human was that of Voronoy (52) who transplanted a kidney into the groin of a patient with mercuric poisoning. The recipient, however, died within two days and no conclusions can be drawn about the survival of the kidney. Landsteiner and Hufnagel transplanted a kidney from a cadaver to the brachial artery and cephalic vein of a young woman in acute renal failure (53) in 1945. However, the patient's own kidneys resumed functioning a few hours after transplantation, and the role of the homograft cannot be assessed. In 1950 Lawler, West, McNulty, Clancy, and Murphy (54) transplanted a kidney into a patient with polycystic kidney disease following removal of one of her own kidneys. There is no evidence, however, that this kidney ever attained any definite function (55). Servelle, Soulle, Rougeulle, Delahaye, and Touche (56) and Dubost, Oeconomos, Vaysse, Hamburger, Milliez, and Lebrigand (57) performed homografts in the human which were reported from Paris in 1951. These kidneys functioned only temporarily although one case of Servelle et al. obtained an output of 600 milliliters by the nineteenth day, when the patient died. Three other cases of kidney homografts between nonrelated humans were reported by Kuss, Legrain, Camey, Desarmenien, Mathé, Nedey, and Vourc'h

(58). None of these functioned for more than short periods of time. The results of Murray and Holden (59) also suggested failure in all their cases of renal transplantation in man. Michon and his associates reported the transplantation of a kidney between mother and son of the same blood groups, following the accidental removal of a single kidney from the recipient (60). This kidney functioned well for 23 days and suddenly ceased to function. Hume, Merrill, Miller, and Thorn reported nine cases of renal homotransplantation in the human in 1955 (61). Six kidneys were obtained from cadavers. In two, the kidneys were removed from living donors in whom nephrectomy was necessary for a surgical procedure leading to the relief of hydrocephalus. In one case the donor kidney came from a patient with a malignant tumor of the lower end of the ureter. None of the kidneys survived permanently in these instances but three of them functioned for a period of one to five and one-half months and attained a function adequate to significantly lower the blood urea nitrogen and to give evidence of marked clinical improvement. Because skin ureterostomies were used and the kidney placed in the thigh of the recipient, infection was a prominent feature of the kidneys at autopsy. The use of ACTH and cortisone was ineffective in promoting survival of the grafts. The kidney which obtained the best function of the longest duration was encaised in a cellophane envelope at the time of transplantation. It is not possible at the present time to say what role was played by this procedure in the prolongation of the homograft. Evidence from these studies when compared with the shorter survival in the dog suggested that the prolongation of renal homografts in humans might be due to a species difference. However, the difference in the histologic picture of the rejected human kidneys and that in dogs may be accounted for partly by infection as a result of skin ureterostomy. In the

case of Michon, in which the ureter was implanted in the bladder, the kidney functioned well for 23 days, and ceased to function abruptly (60). The histologic picture was similar to that of rejected kidneys in the dog, and this case suggests that in the chronic uremic patients reported by Hume et al. (61), the prolonged survival of the homograft might have been due to the effect of uremia per se. This hypothesis is further supported by prolongation of the survival of skin homografts in chronic uremic patients (36). Although all the kidneys in this series ultimately failed, these studies nevertheless showed that transplantation of the kidney in the human was a technically feasible procedure, and that chronic uremia tended to prolong the survival of kidney homografts.

KIDNEY TRANSPLANTATION BETWEEN IDENTICAL TWINS

From the results quoted above it appeared that though there might be quantitative differences in the rejection of kidney grafts in chronically ill man when compared to normal dog, nevertheless, the immune basis for the rejection of kidney homografts was similar to that for other transplanted tissues. The technical and clinical background required in the care of these patients, however, was invaluable in achieving the first successful kidney transplant in man. In 1956, Merrill, Murray, Harrison, and Guild reported a successful renal transplant between identical twins (62). The recipient was a 23-year-old man terminally ill with chronic nephritis and hypertension who had a healthy, and apparently identical twin. It was realized that skin grafts had been successfully transplanted between identical twins and it was known that the rejection of transplanted tissue was an individual rather than an organ-specific response; thus it was felt that if skin could be transplanted between identical twins, a kidney graft might also succeed. In this case a kidney was taken from

the healthy identical twin and transplanted into the right iliac fossa of the sick twin. The renal artery was anastomosed end to end with the hypogastric artery of the recipient and the renal vein end to side with the iliac vein. The ureter was connected directly with the bladder. Urine was elaborated from the transplanted kidney within minutes after completion of the vascular anastomoses. Renal function improved rapidly and within 15 days the blood urea nitrogen was normal. Four months later the right kidney, and six months later the patient's own left kidney, were removed, the transplant alone maintaining chemical well-being. A striking feature of this procedure was the disappearance of the signs and symptoms of malignant hypertension following the transplantation of a third kidney and before the removal of the patient's own two kidneys. Since that time successful kidney transplantation has been accomplished in 14 other sets of identical twins in similar circumstances in our laboratory and in four other instances elsewhere in the United States. Successful kidney grafts between identical twins have also been performed in Canada, Scotland, and France. Seven of our cases have been reported by Murray et al. (12). One of these cases was a technical failure because of a congenital abnormality of the vasculature. Two others have died since operation because their transplanted kidney developed the same disease with which their own two kidneys were afflicted. A third patient has also developed glomerulonephritis in his transplanted kidney but is still clinically well. In a more recent case we have attempted to prevent the development of the nephritic process in the transplanted kidney by removing both the patient's own kidneys prior to transplantation and by subsequent treatment with small doses of cyclophosphamide (Cytoxan) [N,N -bi β -chloro-ethyl] [N^1 -O-propylene-phosphoric acid ester diamid], a nitrogen mustard, which appears to have some effect upon the

suppression of antibody formation. While these results in identical twins were encouraging and suggested that the procedure was technically feasible in man, the results did not help in dealing with the immunologic process by which a true homograft is rejected.

INDUCED TOLERANCE TO HUMAN RENAL HOMOGRAFTS

Previous experience with kidney transplants between nonrelated individuals suggested that some other approach was necessary if one were to modify the immunologic response and enable the kidney homograft to survive long periods. Such an approach was suggested by the success in inducing "tolerance" to tissue by lethal whole body irradiation and bone marrow grafting described previously. The next attempts at kidney transplantation were directed along these lines. A 31-year-old woman from whom a ruptured solitary ectopic kidney had been removed surgically was given 600 roentgens of total body irradiation from a two million electron volt source over a period of three and one-half hours. During the first 48 hours after irradiation she was given 36 billion marrow cells pooled from 11 different donors. On the fourth day following irradiation a renal homograft from a four-year-old female was placed in the right thigh, during which procedure the patient received an additional 170 million marrow cells from the kidney donor. The patient died 32 days after X ray, with both infection and diffuse hemorrhage as prominent contributory causes. However, the transplanted kidney showed no histologic evidence of rejection. A second patient, a 12-year-old boy, had a solitary kidney removed surgically following rupture from trauma. He received 700 roentgens of whole body irradiation and 7.4 billion marrow cells from his mother, followed by a second dose of 3.1 billion. However, in the absence of any conclusive evidence of a successful marrow graft, it was not advisable

to sacrifice one of the mother's kidneys as a homograft. In both these cases death was due to failure of the grafted marrow to survive (63). From subsequent reports of bone marrow grafts following large doses of irradiation for the treatment of leukemia in humans (64), it appeared that bone marrow survival following X irradiation in the human was only temporarily successful.

Since temporary survival of a renal homograft did not justify X irradiation and marrow transplantation in man, a somewhat different approach was next attempted. It has been suggested previously that marked antigenic disparity requires drastic attempts to modify antibody response; with lesser antigenic disparity, however, it seems possible to produce tolerance with lesser doses of irradiation and smaller doses of antigen. This thinking was brought to bear on the problem of transplantation between non-identical fraternal twins, one of whom was chronically ill with uremia. The physical characteristics of the brothers were dissimilar, and skin grafted from the sick to the healthy twin was rejected after a period of 23 days. A second skin graft placed shortly thereafter was rejected in an accelerated fashion, indicating without question that immunity to the transplanted skin had been produced by the first skin graft. Although these twins were not identical, it appeared that they had minimal antigenic disparity as evidenced by the prolonged survival of skin in the healthy twin. Furthermore, the chronic uremia of the sick twin should have made him more tolerant to transplanted tissues. In addition, the transplantation of a kidney, as mentioned above, constitutes a large dose of viable antigen placed in the intravascular route, and all of these factors should tend to produce tolerance for such a graft. It was felt, therefore, that it might be possible further to enhance this tolerance by giving such a recipient total body irradiation in a sub-lethal dose. In this manner antibody-form-

ing cells would be temporarily injured at a time that a large homograft was placed, but the damage should not be such as to require transplantation of marrow. Slow regeneration of antibody-forming tissue in the presence of a large viable replicating antigen should favor the production of tolerance in the same way that such antigen produces tolerance in the developing embryo or neonatal animal. In January of 1959, therefore, 250 roentgens of whole body irradiation were administered to the sick twin and one week later, another 200 roentgens. The right kidney of the healthy twin was transplanted to the patient in the same manner as for identical twins. The kidney began to function immediately and after a stormy course complicated by infection, leukopenia, and thrombocytopenia, and the surgical removal of both the patient's own kidneys, he made a good recovery and was discharged from the hospital with normal renal function from one kidney. Six months later, however, the skin graft placed before irradiation was rejected by the sick twin and at that time he showed hematuria and proteinuria. A renal biopsy showed histologic evidence of an early rejection response. The renal interstitium was infiltrated with round cells. He was again treated with X irradiation (50 roentgens per week of whole body irradiation), for a period of four weeks. Large doses of prednisolone were administered at the same time. The white count dropped to 2,100 per cubic millimeter and irradiation was discontinued. However, his hematuria and proteinuria disappeared and his renal function remained normal. In spite of the total and complete rejection of the skin graft, the patient remains well at this writing, more than two and one-half years following transplantation. Subsequently, Hamburger and his colleagues (65), using essentially the same technique, have transplanted a kidney from a fraternal twin to his chronically uremic sibling, and this procedure has been similarly successful. In

one case 450 roentgens were administered and a kidney transplanted to an adult with acute glomerulonephritis and anuria. The kidney was taken from an infant during the course of an operation for hydrocephalus, which necessitated nephrectomy prior to the anastomosis of the subarachnoid space and the ureter. In this patient, however, the blood groups of the homograft donor and the recipient were incompatible and no renal function was obtained. Autopsy revealed diffuse infarcts throughout the kidney probably as a result of hemagglutination due to the blood incompatibility. In the second case a 13-year-old child received 400 roentgens of whole body irradiation, and a renal homograft from her father, who had the same major blood groups. This kidney functioned well, but the patient died on the fourteenth postoperative day of a fulminating pseudomonas pneumonia. In a third patient a kidney from a 23-month-old child of compatible blood groups was transplanted to a 23-year-old uremic recipient. This graft never attained function because of arterial insufficiency.

Although some success has been achieved in dogs with whole body irradiation and renal homografting with the transplantation of marrow (66), the longest survival of a renal homograft in dog has occurred following the use of 6-mercaptopurine (44). In both the irradiation and drug treated animals death was apparently due to infection and pneumonia. Two human cases have died of infection following renal homografting and the use of 6-mercaptopurine (67).

FUTURE PROBLEMS OF TRANSPLANTATION

From the evidence quoted above it is the opinion of the author that many problems remain to be solved before the modification of the immune response permits successful transplantation of the kidney as a true homograft. It is apparent that the closer the histocompatibility of the donor

and recipient, the more easily tolerance is produced. This means from a practical standpoint that less irradiation or drug must be administered. In totally unrelated individuals modification of the immune responses in such a fashion as to permit the successful transplantation of the kidney requires doses of X irradiation or drug which may produce death from infection. Even with conditions of strictest asepsis where one may prevent environmental pathogens from infecting the patient, organisms present in the intestinal tract may invade other tissues and cause death, as in our own case. It is possible that the dose of irradiation or drug may be spread over a long enough period so that acute injury may not cause death in the immediate postoperative period. This possibility remains to be explored. The use of doses of irradiation large enough to require transplantation of bone marrow has not been feasible until now as a preliminary to renal homotransplantation because marrow "takes" in these circumstances in the human seem to be only temporary. In addition, marrow grafts are fraught with the hazard of the "graft versus host" reaction. Although the development of leukemia or malignancy following the use of whole body irradiation is a potential hazard to the recipient of a successful kidney graft, the available data suggest that the incidence of this complication is low enough so as to be of little import if a life-saving transplant can be accomplished. A major problem in the solution of renal homografting in man remains the procurement of a suitable donor. Our own experience indicates that the donor must be of a compatible blood type and should ideally possess as many compatible blood group antigens as possible. The closer the relationship to the recipient the easier should be the production of tolerance to the kidney. At the present time the availability of suitable kidney donors and the ethical and moral, as well as the immunologic problems

involved, make further experience in this field a slow and difficult process. The preliminary results, however, more than justify the application of the combined skills of the immunologist, the surgeon, and the internist in a continuing effort to make homotransplantation of the human kidney and other tissues a clinically feasible procedure.

SUMMARIO IN INTERLINGUA

Es presentate un revista del stato presente de nostre cognoscentias con respecto al factores que modifica le acceptation o rejeccio de transplantaciones de tissu inter individuos del mesme specie. Le rejeccio de tissu transplantate non pare esser completemente un question de specificitate individual, como il esseva supponite in le passato. Le rejeccio de un transplantate tissu pare depender del formation de anticorpore (de character paucu clar) le qual es stimulate in le recipiente per le exposition a antigeno ab le donator. Le disparitate antigenic inter donator e recipiente determina si e quanto longo le transplantate tissu pote superviver. Le capacitate del recipiente de reager contra le antigeno del donator es etiam un factor, e isto pote esser modificate per drogas e per irradiation X que tende a reducer le potentia del recipiente de formar anticorpore. Le transplantation de renes ha essite effectuate a bon successo inter geminos human identic e in tres casos inter geminos qui non esseva identic. Homograffos human a prolongate superviventia ha essite complete inter subjectos non consanguineos in casos in que le disparitate antigenic non esseva marcante e in que irradiation X esseva usate pro modificar le responsa del recipiente. Le transplantation successose de renes human es non ancora un operation de applicabilitate practic.

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THE MISSING DIMENSION

ANYONE who takes the trouble to look objectively and calmly at the earth and the things on it cannot fail to be impressed with the fact that subatomic systems are organized into atoms, atoms into molecules, molecules into supermolecules, supermolecules into cells, cells into tissues, tissues into organisms, organisms into societies. This increasing complexity is as real as time, as demonstrable as space, and as perceptible as motion. A wise man has no trouble seeing that not only in theory but also in fact there is a vast range of organizational complexity on this earth. I wish to suggest that if organizational complexity is used as a dimension, much that seems chaotic can be brought into a scheme of systematic relations.

The process that has produced ever-increasing complexity has been given a name. We call it "Evolution." As the culmination of evolution a system has developed that is so complex that it is able partially to reflect and, in a limited way, to approximate the organizational complexity of the universe. What I am referring to is the human brain. It is an organized system of ten billion nerve cells. Each cell is a highly organized universe of molecules and atomic particles. The human brain represents as far as we know the pinnacle of organizational complexity on this earth. However, it is only in recent centuries that the brain has acquired the power to look down through the simpler forms of biological organization on which it rests into the organized and relatively unorganized matter which lies at the bottom of the scale of complexity. Only recently has man's self-consciousness become sufficiently developed to let him see that he is, in fact, constructed out of "the dust of the earth"—that he is made of the same physical material as the rest of the universe. Man's awareness of his place in nature is just beginning to dawn upon his intelligence.—FREDERIC A. GIBBS: *The Missing Dimension. Perspectives in Biology and Medicine* 3: 486, 1959–1960, University of Chicago Press, copyright 1960.

THE DREAM ANIMAL

MAN, too, has a curious specialization of a more abstract and generalized type, his brain. If this brain, a brain more than twice as large as that of a much larger animal—the gorilla—is to be acquired in infancy, its major growth must take place with far greater rapidity than in the case of man's nearest living relatives, the great apes. It must literally spring up like an overnight mushroom, and this greatly accelerated growth must take place during the first months after birth. If it took place in the embryo, man would long ago have disappeared from the planet—it would have been literally impossible for him to have been born. As it is, the head of the infant is one of the factors making human birth comparatively difficult. When we are born, however, our brain size, about 330 cubic centimeters, is only slightly larger than that of a gorilla baby. This is why human and anthropoid young look so appealingly similar in their earliest infancy. A little later, an amazing development takes place in the human offspring. In the first year of life its brain trebles in size. It is this peculiar leap, unlike anything else we know in the animal world, which gives to man his uniquely human qualities.

Among other forms of life than man, few marked transformations occurred. Rather, the Ice Age was, particularly toward its close, a time of great extinctions. Some of the great beasts whose intercontinental migrations have laid down the first paths along which man had traveled, vanished totally from the earth. Mammots, the Temperate Zone elephants, dropped the last of their heavy tusks along the receding fringes of the ice. The long-horned bison upon whose herds man had nourished himself for many a long journey of illiterate wanderings, faded back into the past. The ape, whose cultural remnants at the beginning of the first glaciation can scarcely be distinguished from chance bits of stone has, by the ending of the fourth ice, become artist and world rover, penetrator of the five continents, and master of all.

There is nothing quite like this event in all the time that went before; the end of brute animal dominance upon earth had come at last. For good or ill, the growth of forests or their destruction, the spread of deserts or their elimination, would lie more and more at the whim of that cunning and insatiable creature who slipped so mysteriously out of the green twilight of nature's laboratory a short million years ago.

Although there is still much that we do not understand, it is likely that the selective forces working upon the humanization of man lay essentially in the nature of the socio-cultural world itself. Man, in other words, once he had "crossed over" into this new invisible environment, was being as rigorously selected for survival within it as the first fish that waddled up the shore on its fins. I have said that this new world was "invisible." I do so advisedly. It lay, not so much in his surroundings as in man's brain, in his way of looking at the world around him and at the social environment he was beginning to create in his tiny human groupings.

He was becoming something the world had never seen before—a dream animal—living at least partially within a secret universe of his own creation and sharing that secret universe in his head with other, similar heads. Symbolic communication had begun. Man had escaped out of the eternal present of the animal world into a knowledge of past and future. The unseen gods, the powers behind the world of phenomenal appearance, began to stalk through his dreams.—LOREN EISELEY: *The Immense Journey*, Random House, New York, 1957, pp. 109, 111–112, 120.

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EDITORIALS

Sweet Dream or Nightmare?

ELSEWHERE IN THIS ISSUE we have quoted from the writings of two philosopher-biologists, Frederic Gibbs and Loren Eiseley, presenting their characterizations of man's place in time and space. In the long perspective of geologic time and the evolution of living organisms, the emergence of the human race has occurred in but a last instant of time. But compared with other forms of life the human organism that has emerged is unequivocally unique. By evolving that extraordinary organ of integration, the human brain, man has stepped out of the biological course of evolution and into a new level of psycho-social evolution. In this marvelously complex organ that lies between his ears man looks at himself and the universe, reconstructs the past, and dreams dreams of the future. And yet because of the very ingenuity of the human brain, ingenuity in unravelling the secrets of Nature and in unleashing the power of the atom, the question must seriously be asked: Does man have a future? Will he dream sweet dreams or will he go down to oblivion in the hideous nightmare of thermonuclear holocaust?

This is the burning question at this crucial point in the evolution of the human race, for our generation, this year, now. This is the question of agonizing complexities that faces the political leaders of the world. This is the question that not nearly enough ordinary citizens are *really* asking themselves. This is the question that quite literally faces all of us. Will there be a tomorrow?

This is the question asked in *The Lancet* (1) a few weeks ago in a leading editorial

entitled, "Has Mankind a Future?" The editorialist stated the question thus:

Today, because of this accelerating acceleration of knowledge, and of the power that it brings, the question is whether the civilization which man has slowly and laboriously built can avoid disastrous dissolution, and whether our species can escape at least partial extinction by "the misapplication of its own ingenuity."

He goes on to call for a spirit of scepticism that will broaden our outlook and question our certainties, reminding us that no form of human society is wholly good or wholly bad and that every form is sure to change. But convinced as each society is that its own form should endure, does it make sense to support that form by waging a nuclear warfare that can result only in national suicide and in no possible victory for anyone? Further, can such warfare possibly be justified if it jeopardizes not only the two world powers in question but the rest of mankind as well, present and future? Can this generation of men make the decision that may deny life to all future generations? No rational man could answer in the affirmative.

But the rational processes of the human cerebral cortex are often subservient to the instincts, habits, and emotions of the thalamus. Most people find it hard to conceive of nuclear warfare in terms other than those of a slightly larger version of the conventional warfare known in the past, a version that many seem ready to accept. Do enough people really understand what lies behind the simple phrase, "nuclear exchange"? Can any system of bomb shelters and civil defense give any meaningful protection against more than the initial blast, against

the oxygen-consuming fire storm, against the deadly contamination of air, food, and water that will lead to early or lingering death of many now living and to genetic damage and malformation in generations yet unborn? As physicians we are particularly concerned with these matters, and we stand ready to serve our nation and our fellow men to the best of our professional ability. But in all honesty we must admit that the best medical service that we can provide could not possibly cope adequately with the medical aftermath of all-out nuclear warfare. A microgram of prevention is worth a megaton of cure.

Sir Charles Snow (2) in an address on "The Moral Un-neutrality of Science," presented before the American Association for the Advancement of Science almost a year ago, pointed out that the creation and stockpiling of nuclear weapons means that inevitably sooner or later some of them are going to go off. He further made the point that, beyond the question of the morality of their creation, the scientist is morally bound to let his fellow men know the probabilities of the occurrence of nuclear explosions and of the character of their effects on the human population. Surely the physician shares with the nuclear scientist at least this latter responsibility.

But already thinking men the world over understand this great, and perhaps final, crisis that confronts the human race. They recognize the cruel dilemma that engulfs our nation and the West. Each man who does will surely support all constructive efforts to negotiate, to promote disarmament, to aid the under-privileged, to lessen tensions, to increase understanding between the peoples of every nation. Above all it is important that as many human beings as possible really grasp our present predicament, stated so succinctly to the United Nations by President Kennedy (3):

Today, every inhabitant of this planet must contemplate the day when it may no longer be habitable. Every man, woman, and child lives under a nuclear sword of Damocles, hanging by the slenderest of threads, capable of being cut at any moment by accident, miscalculation, or madness. The weapons of war must be abolished before they abolish us.

Perhaps the moral issues before the world are paramount after all. Perhaps the end (peace) is strictly conditioned by the means. Balance of terror and preventive war surely contravene the Golden Rule, and massive retaliation is hardly consistent with the Christian ethic. More pointedly for us as physicians, chemical-biological-radiological warfare clearly breaks the Hippocratic Oath. To quote again from Loren Eiseley (4):

The need is not really for more brains, the need is now for a gentler, a more tolerant people than those who won for us against the ice, the tiger, and the bear. The hand that hefted the ax out of some old blind allegiance to the past fondles the machine gun as lovingly. It is a habit man will have to break to survive, but the roots go very deep.

To do this, the cortex must win out over the thalamus. The hand that lovingly fondles the machine gun now loads the missile and fondles the countdown button. The dream animal with the human brain had better break the habit, and break it soon, or the sweet dream will fast become a nightmare.

J. R. E.

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The Liver and the Brain

THE NATURE OF THE RELATIONSHIP between the liver and the brain is one of the oldest problems in medicine and one that has proved a fruitful source of speculation from the time of Hippocrates to the present day. Space does not permit an historical review of the extensive literature on this subject, nor does the situation require it. It is only in recent years that theory has been replaced by knowledge based on the scientific study of disease. Until scarcely two decades ago the question which bedeviled most writers was the nature and locus of the primary abnormality: Should this be sought in the liver or in the brain? Even a distinction between hepatic encephalopathy and Wilson's disease could not always be clearly drawn (1), and as recently as 1953 Brown's thesis, "Liver-Brain Relationships," was almost entirely confined to a consideration of these two conditions (2).

Increasing specialization in medicine has resulted, more and more, in an uneven distribution of knowledge so that there may be considerable delay before advances made in one field are applied to another. A wide diversity of separate disciplines must be drawn upon by all who garner in the fields of liver-brain relationships, and not the least of these is biochemistry; thus the situation presents both a problem and a challenge which must be met before we can hope to bring our knowledge to completion.

Classification of the various pathological states in which the liver and the brain are apparently related should, to some extent, help to clarify this complex picture. In this task I have, as far as possible, been guided by biochemical rather than clinical considerations hoping that this will throw some light on certain of the unsolved problems which still confront us.

LIVER-BRAIN RELATIONSHIPS

- (1) Enzyme defect in the liver leading to disease of the brain (or nervous system):
 - (a) kernicterus;
 - (b) phenylketonuria;
 - (c) acute intermittent porphyria.
- (2) Generalized enzyme defect leading to disease of the brain and liver:
 - (a) galactosemia;
 - (b) hepatolenticular degeneration (Wilson's disease).
- (3) Primary disease of the liver or hepatic circulation leading to disturbed cerebral function:
 - (a) acute hepatic necrosis;
 - (b) hepatic cirrhosis;
 - (c) portal vein occlusion.

A number of other inherited metabolic diseases in which the predominant picture is one of mental deficiency or abnormal central nervous system function may soon come to be included in the first category but at the time of writing the exact nature and site of the biochemical lesion have not been determined. Such conditions are Hartnup disease (3, 4), Reeves' disease (5), maple syrup urine disease (6), leucine sensitivity (7), fructose intolerance (8), and cystathionuria (9).

To describe in detail the clinical manifestations and biochemical lesions in these various conditions is beyond the scope of this review. All that can be achieved in the space available is to mention briefly the more important advances in each so that the interested reader can seek more detailed accounts from original sources.

(I) ENZYME DEFECTS IN THE LIVER LEADING TO DISEASE OF THE BRAIN

(a) *Kernicterus*: Kernicterus is in truth a syndrome and not a disease, for it may be

due to enzyme deficiency, enzyme immaturity, or excess hemolysis of whatever etiology. All, however, have this in common, that the conjugating enzymes in the liver are unable to handle the bilirubin load presented to them in the first days of extrauterine life. In normal conditions free bilirubin reaches the hepatic parenchymal cells as a result of red cell breakdown in the spleen and reticuloendothelial system. In the liver the lipophilic pigment is conjugated to form water soluble mono- or di-glucuronides or sulfates. Because in the new born infant the enzyme glucuronyl transferase has only 1 or 2% of the normal adult activity, any abnormal load of bilirubin can result in a dangerous accumulation of this pigment in the blood; being lipophilic the free bilirubin enters the immature brain where its action as an uncoupling agent for oxidative phosphorylation may interfere seriously with the energy supplies of the neurones (10). The most common cause of such an abnormal bilirubin load is Rh incompatibility but other hemolytic anemias can lead to a similar course of events. In premature infants the enzyme system may be completely inactive and even physiological rates of bilirubin production can lead to dangerously high concentrations of unconjugated pigment. A rare variety of kernicterus is associated with congenital (and presumably genetically determined) absence of the transferase enzyme (11, 12); an analogous condition is known to occur in rats (13).

(b) *Phenylketonuria:* In this genetically determined metabolic disease the missing enzyme is phenylalanine hydroxylase: it is normally present only in the liver and is necessary for the irreversible parahydroxylation of phenylalanine to tyrosine (14, 15). In consequence the normal metabolic pathway for phenylalanine is blocked and the amino-acid appears in the plasma and urine in very high concentrations. In addition the urine contains much phenylpyruvic acid, phenyllactic acid, and phenylacetyl

glutamine together with certain orthohydroxy phenolic acids and indolyl compounds. These latter may account for loss of as much as 50% of the dietary tryptophan intake (16) although the daily output of 5-hydroxy indolylacetic acid is less than normal. The pathogenesis of the brain damage is obscure but current theory does not support the hypothesis that excess phenylalanine itself exerts a direct toxic action on the brain. However, the excess of this amino-acid might have an indirect toxic action by causing general intracellular amino-acid imbalance or by interfering with the further oxidation of tyrosine. The relationship of the high concentrations of phenylalanine to disturbances of tryptophan metabolism and the role of the abnormal indolyl metabolites also remain to be elucidated. However, the favorable biochemical and growth response to early restriction of phenylalanine in the diet now appears to be established (9).

(c) *Acute Intermittent Porphyria:* Probably other porphyrias should also be included in this category, such as the variegate porphyria of the South African Dutch (17). The role of the liver in the pathogenesis of these conditions and the nature of the enzymatic defect are not yet known. In acute intermittent porphyria the most obvious biochemical abnormality is the excretion of large amounts of porphobilinogen and δ -aminolevulinic acid in the urine (18, 19) during acute attacks. Porphobilinogen is probably formed in the liver and at post-mortem is regularly found there in considerable concentration in patients dying of acute intermittent porphyria. There is no evidence that the conversion of porphobilinogen to heme is defective in these patients and it has been assumed that the abnormality is one of over-production rather than a block of further metabolism of this compound. Over-production of porphobilinogen may itself be secondary to an excess of δ -aminolevulinic acid in the liver which has accumulated following a block

in one of the alternate metabolic pathways for the latter compound. Attacks of acute intermittent porphyria are often precipitated by the administration of barbiturates to susceptible subjects though the mechanisms involved are unknown; so also is the nature of the "toxic factor." There is no evidence that either porphobilinogen or δ -aminolevulinic acid has significant pharmacological effects in experimental conditions (20).

(2) GENERALIZED ENZYME DEFECTS RESULTING IN DISEASE OF THE BRAIN AND LIVER

(a) *Galactosemia*: This is perhaps the best understood of all hereditary metabolic diseases affecting the liver and the brain. It is transmitted as a mendelian recessive trait and, like phenylketonuria, heterozygotes for the abnormal gene can be identified by their response to a metabolic load. The missing enzyme, galactose-1-phosphate uridyl transferase (20), though normally present in highest concentrations in the liver, is also found in other tissues, as for instance, the erythrocytes. The inability of the red cell to metabolize galactose is used as a diagnostic test for the disease.

Inability to convert galactose to glucose need not be disastrous to the adult but leads to dire consequences in the new born infant, dependent as he is on lactose for the supply of carbohydrate. The biological significance of galactose in the lactose molecule is not clear but as development can proceed normally in galactosemics on a galactose-free diet it may be of teleological rather than immediate biological importance. In any case the presence of this sugar in the diet of an individual lacking the necessary transferase results in high blood and tissue levels not only of galactose itself but also of galactose-1-phosphate. It is probably the presence of this latter compound in the tissues which leads to a widespread breakdown of carbohydrate metabolism by competing with glucose-1-phosphate for active centers on the enzyme phospho-

glucomutase, thereby depleting the tissues of glucose-6-phosphate and depriving them of their main energy supply. This explanation is in keeping with the widespread damage to diverse organs such as brain, liver, kidney, and lens.

(b) *Hepatolenticular Degeneration (Wilson's Disease)*: The missing protein or enzyme in this disease is the serum copper protein ceruloplasmin. This is an α -globulin of molecular weight 151,000 each molecule containing 8 copper atoms which are probably arranged in functional pairs (22). The absence of this protein is associated with copper storage in many organs but most notably the brain and liver. *In vitro* copper is a powerful enzyme poison and introduction of as little as 15 to 20 micrograms in the theca will cause convulsions and death of pigeons. There is evidence to support the theory that the metabolic block produced in these conditions is by oxidation or chelation of the dithiol lipoic acid. In consequence pyruvate is not oxidatively decarboxylated and therefore cannot enter the Krebs cycle (23). Such a biochemical lesion is certainly in keeping with the known affinity of copper for sulphhydryl groupings. The delayed onset of symptoms in the patients for ten to 20 years after birth would depend in part on the amount of copper in the environment and in part on the non-specific binding of copper by many tissue proteins. Only when these are saturated can the metallic ion enter the cell nucleus and inactivate vital enzyme centers on the mitochondria.

The role played by ceruloplasmin in maintaining normal copper balance is not understood but it is of interest that the new born baby, like the adult with Wilson's disease, has a low serum level of ceruloplasmin and a high concentration of copper in the liver. During the third month of extrauterine life the concentration of metal in the liver falls at the same time as ceruloplasmin synthesis reaches adult levels. Though this evidence is circumstantial it

does support the theory that ceruloplasmin is, in some way not understood, directly concerned with either mobilization or control of tissue copper levels. Richterich (24) has reported finding two functionally distinct ceruloplasmins: a storage protein present in the liver from birth and a transport protein synthesized from the former by the action of a kinase. This kinase is absent or immature in the infant liver and the liver of patients with hepatolenticular degeneration. The relationship of this protein to copper binding protein isolated from human liver by Morell, Shapiro, and Scheinberg (25) has yet to be established. The major difficulty in attributing a leading role to ceruloplasmin deficiency in Wilson's disease has been the occasional finding of otherwise typical cases of the disease with normal concentrations of this protein (26). Moreover, it has not hitherto been possible to demonstrate any functional abnormality in this protein by estimation of the copper-protein complex (blue color), antigenic site, or catalytic center. Study of this latter parameter has been complicated by our ignorance of the physiological substrate of the enzyme or indeed the lack of evidence for any enzymic function in the intact animal. Recently Walshe and Briggs (27) have shown that the ceruloplasmin of patients with Wilson's disease may differ from normal ceruloplasmin when tested for oxidase activity in the presence of enzyme inhibitors. This suggests that these patients may not in fact be deficient in this specific protein but that they are synthesizing an abnormal protein with reduced oxidase activity and possibly also reduced copper content. Such a hypothesis, if it could be substantiated, would bring Wilson's disease into line with the hemoglobinopathies as a disease of abnormal protein synthesis rather than a condition in which there is a complete failure of production due to absence of the template on which the peptide chains of the protein are normally constructed.

(3) GENERALIZED DISEASE OF THE LIVER, OR
HEPATIC CIRCULATION LEADING TO AB-
NORMAL CEREBRAL FUNCTION

The coma of acute hepatic necrosis, hepatic cirrhosis, and the encephalopathy resulting from shunting of portal vein blood past the liver will not here be considered separately. These particular aspects of liver-brain relationship have received much attention in the past decade although they have not yet reached a final solution. I have reviewed in detail elsewhere recent work and theories on the nature and locus of the biochemical lesion (28); only the more outstanding points will be touched upon here. One feature common to almost all examples of hepatic coma is the raised level of blood "ammonia" and evidence is at last available that the volatile base is indeed ammonia (29). Bessman, Fazekas, and Bessman have postulated that the excess ammonia depletes the brain's reserves of α -ketoglutarate, a necessary intermediate in the Kreb's cycle (30). At present there is no published information on the concentrations of this keto-acid in the brains of patients dying of hepatic coma but indirect evidence, from study of blood keto-acid levels, does not support this theory as the concentrations of pyruvate and ketoglutarate are commonly elevated rather than depressed in hepatic coma. However, the almost invariable association of hyperammonemia with hepatic coma and the ability of ammonium salts to precipitate coma in susceptible patients strongly support the contention that disturbances of ammonia metabolism are, in some ill-understood manner, involved in the genesis of coma. The role of susceptibility to ammonium salts has not perhaps received the attention it deserves for there is good evidence that the normal brain can tolerate ammonium loads which prove toxic to patients with hepatic disease (28, 31). Evidence for increased susceptibility to ammonium ions has also been adduced from

in vitro studies on the brains of rats with chronic liver damage (32). Other factors are almost certainly involved such as disturbances of indole and serotonin metabolism (33, 34), and deranged metabolism of the sulphur amino-acids leading to the production of potentially toxic mercaptans and alkyl sulphides (35). In addition changes in blood pH may be of considerable importance for alkalosis, commonly present in hepatic coma, may result in increased permeability of the blood brain barrier to ammonia (36, 37).

CONCLUSIONS

In this brief review scarcely any mention has been made of the protean clinical manifestations of these various metabolic disturbances nor has any account been given of the morbid anatomical changes to which they may give rise. Some are so subtle as to defy detection by modern histological techniques; others, as in hepatolenticular degeneration, may lead to widespread necrosis and cavitation in the brain.

Perhaps one final generalization may be permitted. The time has now surely come to discard the out-dated conception of a "liver-brain relationship," a thing apart as it were, which simply awaits codification and definition at the hands of the appropriate scientific genius. Such thinking is naive. The foregoing pages must surely have made clear the scope of the problem. The brain is dependent on the liver for the provision of the necessary biochemical background upon which it can achieve the full range of its integrative actions. Failure at any one point in an enzyme chain will produce its own particular failure of cerebral function. Thus we can observe the complete spectrum of disordered relationships from the highest cerebral functions of conceptual thought, as in the metabolically determined mental deficiencies, through disturbances of motor function, as in Wilson's disease and kernicterus, to simple failure of conduction along the peripheral nerves, as in acute

intermittent porphyria. It seems unreasonable to expect or to hope that new advances will simplify this picture, for as yet more enzyme systems are isolated and defined so must we expect to add to our list of "liver-brain relationships."

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BOOKS

Book Reviews

Thoracic Diseases: Emphasizing Cardiopulmonary Relationships. By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P., and MORRIS RUBIN, M.D., F.A.C.S., F.C.C.P., in association with GEORGE C. LEINER, M.D., F.A.C.P., F.A.C.C., and DORIS J. W. ESCHER, M.D. 968 pages; 26 × 19 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$25.00.

The various subspecialties of internal medicine have come to be covered by special texts which supplement the general textbooks of medicine and which lead the reader into the journal literature of their respective areas. In 1947 Dr. Eli Rubin published his *Diseases of the Chest*, which became recognized as one of the two or three best texts in the field of pulmonary diseases. Since that time the study of chest diseases has expanded prodigiously and now is far more solidly based on pulmonary anatomy and physiology than it had been. In recognition of this expansion Drs. Eli and Morris Rubin have so extensively revised the original text that they offer, in effect, a new book, *Thoracic Diseases, Emphasizing Cardiopulmonary Relationships*.

Note the excellencies of *Thoracic Diseases*. The descriptions of disease are complete and accurate, and are adequately illustrated with X rays. Each section is followed by an intelligently arranged bibliography that includes both classic and recent references. Because of the unified authorship, inconsistencies and omissions are avoided. The frequent references to case material give a feeling of authenticity to the text and enable the less knowledgeable reader to relate descriptions to his own experience. Dr. Eli Rubin has been particularly interested in the pulmonary manifestations of systemic diseases; this section of *Thoracic Diseases* is outstanding. New disease states, for example pulmonary alveolar proteinosis, are adequately covered, but not to the detriment of an extensive treatment of tuberculosis and bronchogenic carcinoma.

The first quarter of *Thoracic Diseases* surveys the anatomy and physiology of the chest. This section is only a survey. The general

reader will use it to construct in his mind a skeleton of clinical cardiopulmonary physiology and will then progress to Comroe's classic *The Lung* and the journal literature.

Can one pick defects in *Thoracic Diseases*? There are very few. The section on physiology of symptoms (e.g., chest pain, dyspnea) is short and is not in proportion to the importance of these subjects to the man who must analyze patients and their stories. Should bronchiectasis be classified as an obstructive disease? Many cases show little evidence of obstruction physiologically, and the pathogenesis in most instances is obscure. The classification given here may be misleading in the sense that it suggests a close relationship of bronchiectasis to asthma and to emphysema.

In general, however, *Thoracic Diseases* is a splendid book, the product of considerable labor. It will undoubtedly appear on private and institutional library shelves as a leading monograph in its field.

ROBERT W. CARTON, M.D.

Chest Pain. Systematic Differentiation and Treatment. By NATHANIEL E. REICH, M.D., and RUDOLPH E. FREMONT, M.D. 366 pages; 23.5 × 16 cm. The Macmillan Company, New York, 1961. Price, \$9.00.

The symptom of chest pain, certainly one of the most common complaints presented to the general practitioner, internist, and chest physician, is frequently a very difficult diagnostic problem. This book makes the physician aware of the great variety of disorders which can cause chest pain, and leaves him with little doubt that chest pain will continue to be a frequent diagnostic problem. With the rising incidence of heart disease, the differentiation of this cause of chest pain from that caused by other disease processes will be even more important.

The authors have given us a systematic program for the investigation of the causes of chest pain, using the most logical approach, that is, from the standpoint of the anatomic site of the disease causing the pain. In the first two chapters, they suggest an approach to the diagnosis

of chest pain and discuss the anatomy of chest pain. Then, in the following twelve chapters, the many causes of chest pain are discussed from the anatomic approach beginning with chest wall pain and moving to diseases of the inner structures of the thorax, the diaphragm, and the abdominal conditions causing chest pain. Some of the disorders causing chest pain are mentioned very briefly and many are discussed at length. Usually the authors have included something about the pathophysiology of the disease, mechanism and characteristics of the chest pain, aids in diagnosis, and treatment. Fortunately they have weighed the material carefully and the more common diseases receive more attention. The discussion of treatment is adequate for many of the diseases, but inadequate for others, and the reader will need to turn to other reference books for this information. The book is attractive, well arranged, printed on good quality paper, provided with well reproduced illustrations, and, therefore, easy to read. There is a very good bibliography at the end of each chapter.

The authors have accomplished their purpose of providing a book on the systematic differentiation and treatment of chest pain for the physician who is involved in the diagnostic problems of chest pain. Unique is the systematic method with which the many causes of chest pain are discussed. It deserves a place in the library of the physician who encounters symptoms of chest pain frequently, particularly the general practitioner, internist, cardiologist, and chest physician. Medical students and house officers, too, can obtain much useful information from this work.

JOSEPH C. ROSS, M.D.

Physiology of the Digestive Tract. By HORACE W. DAVENPORT, PH.D., D.Sc. (Oxon.) 221 pages; 26 x 18.5 cm. Year Book Medical Publishers, Inc., Chicago, 1961. Price, \$8.50.

This monograph represents the first attempt in recent years to present the physiology of the digestive tract in a single volume. The author states clearly that his purpose is "to make the basic facts of gastroenterological physiology readily available to medical or graduate students who are beginning their study of the digestive tract." This has been done in a very readable fashion. The page design, graphs, tables, and illustrations have all been done in a clear and easily read form. Dr. Davenport's justly famous wit appears frequently enough to make the text pleasurable as well as informative.

The book is divided into three sections: motility, secretion, and digestion and absorption. The secretion of bile is considered along with that of the salivary glands, pancreas, and the intestinal glands. Matters of historical interest are mentioned sparingly, while emphasis is placed on the present state of our knowledge. With few exceptions the details of the techniques by which this knowledge was obtained are omitted. There is a selected bibliography at the end of the book consisting largely of classic reviews. The index is satisfactory.

Much of the current modest renaissance in digestive physiology has come about through the efforts of investigators interested primarily in membrane phenomena, i.e., the secretion of hydrochloric acid, bile and pancreatic juice, the fluxes of various substances across the intestinal membrane, the properties of intestinal smooth muscle and neuromuscular transmission. The use of isotopes, the measurement of intracellular and extracellular electrical potentials, the recording of intraluminal pressures, and the use of chromatography and ion exchange columns in the analysis of digestive fluids have advanced our knowledge of gastrointestinal physiology while introducing a new terminology. The significance of these developments is discussed in this monograph. In a rapidly advancing field, it is inevitable that even a monograph will lag behind current concepts. Dr. Davenport has restricted himself to generally accepted material.

The internist who will put himself in the place of a student being introduced to digestive physiology will find this monograph to be a lucid presentation of current knowledge in a form which he should be able to follow without undue effort. Clinical applications are mentioned infrequently and scantily, so that the book should be read for a background in physiology and not as a study of pathologic physiology. For the specialist in gastroenterology, the monograph leaves something to be desired, bearing in mind the author's clear statement of his purpose. It might be thought that a reading of the monograph would equip one to read current original research articles with considerable insight. This reviewer believes that physicians will not find this to be the case unless they are already familiar with the techniques used. The monograph is not likely to help the reader sense the amount of work and intellectual ferment going on in the laboratories of Davenport, Hollander, Davies, Rehm, and Hogben in the field of gastric

secretion, of Isselbacher and Wilson in absorption, or of Ingelfinger, Code, Texter, Ferrar, and Hendrix in motility.

The physician concerned with a research problem who looks for a bibliography to give him a background of information bearing on a specific subject will not be likely to find this book useful. On the other hand, the internist preparing himself for subspecialty examinations in gastroenterology should find it to be very helpful.

For comparison with Davenport's monograph, the chapters on gastrointestinal physiology in the textbooks edited by Best and Taylor, and by Bard (1961 editions), should be considered. Professor J. Earl Thomas in the Best and Taylor has written a carefully documented account of the development of gastrointestinal physiology with considerable emphasis on the relation of structure to function. The regulation of food intake is discussed and an entire chapter is devoted to visceral sensations. Professor E. S. Nasset in the Bard edition has devoted considerable space in a relatively short section on gastrointestinal physiology to digestion as compared with secretion and absorption. Neither of these two authors has a chapter on smooth muscle comparable to that in Davenport. Nasset's section is thoroughly referenced and the quality of paper and illustrations is excellent.

Other monographs have been planned for the various subspecialties in physiology and these may represent the introductory text of the future. Perhaps the *Handbook of Physiology* now being published by the American Physiological Society will serve as the source of reference for those physicians who need more detail. This reviewer believes that the internist who desires a firm command of current gastrointestinal physiology would do well to supplement the present monograph with reading in a text of general physiology such as that by Davson or Bayliss.

FRANK BROOKS, M.D.

Transactions of the American Society for Artificial Internal Organs. Vol. VII. Edited by GEORGE E. SCHREINER, M.D. 391 pages; 28 x 24 cm. Georgetown University Printing Department, 1961. Copies may be ordered from George E. Schreiner, M.D., Department of Medicine, Georgetown University Hospital, Washington 7, D. C. Price, \$8.00.

For the physicians and allied scientists who wish to keep abreast of latest developments in organ substitution or augmentation by man-

made devices, the *Transactions of the American Society for Artificial Internal Organs* performs a unique and invaluable service. No other publication presents in comparable breadth and depth current progress and problems in this up-and-coming area of medical engineering. Beginning in 1955 as a modest series of mimeographed papers which failed to qualify for medical indexing, each successive volume of the *Transactions* reflects the rising stature of this young Society and the disciplines to which its members have contributed so significantly. At the present time few American authorities in this field do not belong to the A.S.A.I.O., and its official publication has become recognized as their primary communication medium.

Volume VII records the fifty-four papers presented at the 1961 Annual Meeting in Atlantic City. The majority deal with either hemodialysis or extracorporeal blood gas exchange. In addition, recent work in the following areas is presented: blood pumps (both extracorporeal and intracorporeal), cardiac valve replacement, cardiac pacemakers, induced hypothermia, and human kidney transplantation. As in previous years, this issue contains much useful data on new hardware, techniques, and clinical experience. For example, eight papers are devoted to the use of indwelling arterial and venous cannulas for repeated hemodialysis without repeated surgery, an approach introduced by Scribner which holds great promise in the treatment of chronic uremia. Several new models of experimental artificial hearts are described, the mechanics and electronics of which appear to be approaching a level of competence required for human application. Energy transmission across the chest wall and the application of microsurgery to organ transplantation are but a few of the new concepts presented.

Notable also in Volume VII is the considerable attention directed toward critical evaluation of what actually happens, both good and bad, inside the artificial organ and in the organism to which it is attached. Many of the papers present explorations into the physiology, or perhaps "artiphysiology," of extracorporeal devices. As stated in the *Introduction*, the reader will discern throughout these 387 pages "a continuing search for the means whereby all our procedures can be quantitatively measured and continually criticized." Illustrative of this search are studies of the bacteriology of continuous flow hemodialysis, observations on myocardial edema, pulmonary

congestion, acid-base disturbances, and electroencephalographic changes attending extracorporeal blood oxygenation, measurements of organ blood flow during induced hypothermia, and the effect of deep hypothermia on myocardial metabolism. One senses from the reports of these investigations that the art of organ substitution is fast becoming a science.

The offset printing, in two type sizes, affords ease of reading. Illustrations and graphs are reproduced clearly. Bibliographies are generally extensive. Discussions of each paper, recorded from tape with minimal editing, retain an air of freshness and spontaneity.

LEWIS W. BLUEMLE, JR., M.D.

Basic Biochemistry. By M. W. NEIL, PH.D. 360 pages; 22.5 × 14.5 cm. J. B. Lippincott Company, Philadelphia, 1961. Price, \$6.75 (North American market).

Textbook of Biochemistry. 3d Ed. By EDWARD STAUNTON WEST, PH.D., and WILBERT R. TODD, PH.D. 1,423 pages; 24 × 16 cm. The Macmillan Company, New York, 1961. Price, \$16.75.

Designed for use by medical students during their course in the subject, these two texts differ in every other respect. *Basic Biochemistry* is a short book, well written, and covers almost all of what might be regarded as mammalian biochemistry. Topics such as photosynthesis have been omitted. Inevitably, in a book of this type, some topics are treated sketchily and the material in some areas is sadly out of date. For example, the biosynthesis of the fatty acids is covered in two short paragraphs and no mention is made of the role of carbon dioxide, biotin, or malonyl coenzyme A. Intermediary metabolism in general does not receive sufficient attention. In spite of these shortcomings, this book should be quite useful for physicians wishing to improve their general biochemical knowledge, but it is not recommended as a reference source. In fact, there are no references to original literature at all. A judicious selection of such references would do much to ameliorate the rather cursory treatment given to many fields.

Textbook of Biochemistry by West and Todd goes to the opposite extreme. The third edition, like the preceding ones, is almost encyclopedic. Every area of modern biochemistry is well covered and it is as up to date and reliable as a textbook can be. This is an excellent book and it has been one of the leading texts in this country for many years. Its drawbacks stem from its size. This is not an easy

book to read and the beginning student has every right to feel overwhelmed (after recovering from the shock of discovering the price). For the graduate student or the physician, however, it is an excellent reference source for those with more than a casual interest in biochemistry. One cannot help feeling, however, that there ought to be a good biochemistry textbook somewhere in between the two extremes represented by these volumes.

JULIAN B. MARSH, M.D.

The Dreams of Reason. By RENE DUBOS. 167 pages; 23 × 15 cm. Columbia University Press, New York, 1961. Price, \$5.00.

In my file on *Humor in Science* is a cartoon which shows three scientists looking at a small pile of gray powder labeled "dehydrated elephant." One of them remarks, "Even if it isn't salable, it proves what a lot of money and research can do." In a crude way, this quip holds the germ of problems considered in Dr. Dubos' essays, presented at the Brookhaven Laboratory as *The Pegram Lectures*.

"Salable" implies a customer. Science is one species of creative action, and creation implies a product. Is the aim of science to produce goods and methods for the benefit of man? Or is it to ever renew and, hopefully, deepen man's view of his world? Dr. Dubos opens his reflections on the limits of science with an account of the views of Francis Bacon who as "the first statesman whose aim it was to organize human life in terms of a master plan framed by scientific thought" made the "eloquent and passionate affirmation that science would become a great social force." Whether Bacon took his tune from incoherent murmurs already buzzing in his times or composed a new theme to be played out by later generations, is not the main concern of Dr. Dubos when he considers the probable influence of Bacon on his successors. Dr. Dubos' point is that

It was the richness and convincing beauty of Bacon's language that made the world at large take notice of scientific knowledge as an instrument of power and of social growth, thus launching us on the road that we are still travelling today. No one questions any longer the fact that science is increasing the dominion of man over nature. This does not mean, of course, that man will uncover through scientific technology the happiness that Adam knew before the Fall, as Bacon hoped. But Bacon certainly contributed to

the modern world its most characteristic aspect and its most lasting illusion when he created his utopia of happiness based on application of scientific knowledge.

One of the illusions to which Dr. Dubos refers is the expectation that science, in the cloak of medical research, will rid man's world of disease. Though the layman labors more under this hope than his medical brother (when he considers the host of genetically-conditioned diseases), even the investigator may take it in unconscious faith too and may imply, if not say, to his lay friends that "a lot of money and research can," to borrow words from the cartoon, wipe out cancer, or heart disease, or whatever ills will succeed these scourges when they have fallen before the forces of medical research. Perhaps some scientists have sustained this particular illusion for man because it is an eminently "salable" product, one that keeps the scientists in business.

In the penultimate essay, "The Dehumanization of the Scientist," Dr. Dubos reflects on causes for anti-science. He suggests that scientists, by failing "to emphasize the disinterested aspects of knowledge" and by ignoring "the fact that today, as in the past, men starve for understanding almost as much as for food," may be throwing fuel on the fires of anti-science. But do most men want the kind of understanding and the freedom of spirit which science can offer? This understanding and this freedom of spirit are banners behind which science marches not to a home of certainty but in a perpetual wandering and questioning. And isn't this uncertainty and restlessness of mind the quality of science most truly repugnant to the anti-scientist? Remember the words of The Grand Inquisitor in Dostoyevsky's *The Brothers Karamazov* as he addresses Christ:

Freedom, free thought and science, will lead them into such straits and will bring them face to face with such marvels and insoluble mysteries, that some of them, the fierce and rebellious, will destroy themselves, others rebellious but weak, will destroy one another, while the rest, weak and unhappy, will crawl fawning to our feet and whine to us, "Yes, you were right, you alone possess His mystery, and we come back to you, save us from ourselves!"

The understandings that science offers are not the answers which most men crave; if

science offers such answers, it will no longer be science, and scientists will have shed white coats for priestly robes.

Dr. Dubos has put his reflections into clear and graceful prose. His publishers have given his essays handsome carriage, with brilliant typography and elegant reproductions of the portraits and prints which illustrate his text. I should have preferred hearing Dr. Dubos speak his words in his supple but sure voice, but reading them was hardly less a pleasure.

EDWARD J. HUTH, M.D.

The Myth of Mental Illness: Foundations of a Theory of Personal Conduct. By THOMAS S. SZASZ, M.D. 337 pages; 24 × 16 cm. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York, 1961. Price, \$7.50.

Using conversion hysteria as a paradigm, this book elaborates the concept of mental illness as a psychosocial disorder which can be understood only in terms of the interplay of the patient, his social environment, and the physician.

Mental illnesses are communicative actions, to be understood in terms of motives, rule following, and the like, and hence inevitably involving moral judgments, in contrast to bodily disorders which happen to the patient, and are to be understood in terms of conventional causality. Hysterical symptoms are analogous to primitive picture language, in which the link between symbol and referent is similarity. The hysterical impersonates a person with organic disease in an effort to coerce help by a display of suffering and helplessness, thus resembling the child vis à vis his parent. The physician, by yielding to this coercion—to which he is predisposed by the Judeo-Christian ethic which regards suffering and helplessness as legitimate claims on others—fosters this unhealthy pattern of dominance and submission instead of the more mature one of equality and reciprocity.

Pursuing this theme, Szasz links hysteria, and by implication all mental illness, to lying, cheating, malingerer, and other forms of covertly changing the rules of the game. Although he accepts the fact that the hysterical is not doing this deliberately, his attitude is implicitly derogatory. This may be, in part, a justified reaction to the current sentimental tendency to regard all forms of deviant and antisocial behavior as forms of illness warranting treatment rather than punishment, but the effort to assimilate mental illnesses to misbehavior rather than illness seems somewhat overdone.

This point illustrates Szasz' tendency to raise throughout his book interesting and far-reaching issues without clarifying them. For example, he never adequately explores his somewhat dubious premise that conversion hysteria is a paradigm for all mental illness. Nor is his identification of illness with bodily disorder, on which he bases the sharp distinction between medical and mental illnesses, critically examined. In the reviewer's opinion, it is untenable. Humans are subject to a variety of stresses emanating from derangements of bodily processes, physical, chemical and bacteriological agents, and disturbances in their psychosocial environments. In certain circumstances, which are only beginning to be elucidated, they respond by becoming ill; that is, by assuming the role of patient.

Bodily disorder, though it frequently accompanies illness, cannot be equated with it. A person with asymptomatic lung cancer becomes a patient only after it is diagnosed. Of two persons with equally reduced cardiac reserve, one may be a chronic invalid and the other a normally functioning member of society. The interchangeability of bodily and mental illness is suggested by the finding that both tend to occur in the same persons, and in a given person's life tend to cluster during periods when he perceives his environment as stressful. All patients, whether mentally or medically ill, use symptoms as forms of communication, and their choice of these will depend not only on the condition of their bodies but on previous life experiences, familial attitudes towards illness, moral fibre, and so on. Bodily and mental illnesses are two ends of a continuum. Clarification of the similarities and differences between them is much to be desired, but to exaggerate their differences is as little conducive to progress as to minimize them.

In developing his thesis the author parades his wide erudition, covering among other topics communications theory, Russell's theory of logical types, and games theory. Some of this material is highly informative and stimulating, especially his historical account of the social and personal determinants influencing Charcot to create hysteria as a clinical entity, but much of it seems included more to impress than to enlighten the reader, resulting in considerable repetitiveness and discursiveness.

As chronic illnesses come to occupy an ever-increasing proportion of medical practice, successful care of the patient requires more awareness of the psychosocial determinants and functions of the "sick role" than most physicians

now possess. Although this book may serve as a provocative introduction to this important area, it should be read with due allowance for the author's propensity to draw sweeping conclusions from inadequately analyzed premises.

JEROME D. FRANK, M.D.

Evaluation and Management of the Brain-Damaged Patient. By JEROME S. TOBIS, M.D. and MILTON LOWENTHAL, M.D. 109 pages; 23.5 × 16 cm. Charles C Thomas, Springfield, Ill., 1960. Price, \$6.00.

This book has been written to be uniquely practical and valuable to all physicians who treat patients with brain damage. Presumably these physicians would include neurologists, neurosurgeons, and those interested in physical medicine. I believe that the authors have fallen short of their goals. They dispose of the theoretical aspects of brain function and dysfunction in twenty-three pages by presenting data which are in part controversial, and by using diagrams which are at times grossly oversimplified or difficult to understand. In the section on neurological evaluation of patients with brain damage, the presentation is much more lucid, and the succeeding chapters on management are written with an authority that gives the book its chief worth.

The authors have tried to cover too much material in too short a monograph. Physicians looking for an authoritative work will be disappointed, but persons working in the paramedical fields of physiotherapy, psychology, or nursing should derive benefit from a careful reading of this book.

JAMES F. TOOLE, M.D.

Standard Nomenclature of Diseases and Operations. 5th Ed. EDWARD T. THOMPSON, M.D., F.A.C.H.A., Editor; ADALINE C. HAYDEN, C.R.L., Associate Editor. 964 pages; 22 × 15.5 cm. Published for the American Medical Association by the Blakiston Division, McGraw-Hill Book Co., Inc., New York, 1961. Price, \$10.50.

Some say, however, that (Procrustes) used only one bed, and lengthened or shortened his lodgers according to its measure.

—Robert Graves, *The Greek Myths*, Penguin Books, Baltimore.

To borrow the pattern of a famous quip, one might say of the *Standard Nomenclature* that it pleases some of the doctors some of the time but none of the doctors all of the time.

This fifth edition again uses the scheme of classification based on the site of the disease and its cause. Disease entities delineated since the fourth edition have been added; some diagnoses which should have been tossed out remain. For example, "Milkman's syndrome," which now means no more than the pseudo-fractures or Looser's zones which may appear in the osteomalacias of various origins such as renal tubular acidosis and familial hypophosphatemia (or "vitamin D-resistant" rickets), and in adults with hypophosphatasia, is still appended to "200-9x9, osteomalacia due to unknown cause." Better had it been banished to "2-Supplementary Terms." The term "nephrosis" is sprinkled freely through "Diseases of the Kidney" even though Jean Oliver and other equally competent critics have been doing their best for some years to kill this term. Certainly, nephrologists will writh when they are forced to code acute tubular necrosis due to mercury poisoning as "713-300.9, Nephrosis due to exogenous poison."

How can one code Albright's "tubular-insufficiency-without-glomerular-insufficiency" now better known as renal tubular acidosis? As "713-700.9, Nephrosis due to disorders of metabolism"? How cystinuria—as a disease "due to genetic and prenatal influences, 719-061, Calculi, renal, congenital"?

These samples of defects in one section of the *Standard Nomenclature* show how this current edition (and earlier editions) manage to suit the needs of most doctors most of the time, namely, by holding to a mean orthodoxy of nosologic views.

At least, *Standard Nomenclature* has the virtue of some elasticity. "Senile" osteoporosis can be classified as "2-770, Osteoporosis of bone due to endocrine disorders" if the coder subscribes to the Albright-Reifenstein doctrine of etiology, or as "200-947, Osteoporosis, idiopathic" or "22-798, Senile osteoporosis" if the coder either has no convictions on etiology or subscribes to the newer and not yet orthodox views of Nordin, Fraser, and others relating this disorder to a suboptimal intake of calcium through life.

So, *Standard Nomenclature* offers a diagnostic bed in which most diseases can lie, but a few can be fitted only after a Procrustean violence to the concepts that define them.

EDWARD J. HUTH, M.D.

Annual Review of Medicine, Vol. 12. Edited by DAVID A. RYTAND, M.D., with WILLIAM P. CREGER, M.D., Associate Editor. 455 pages; 23 x 16 cm. Annual Reviews, Inc., Palo Alto, California, 1961. Price, \$7.00.

Serial reviews of recent advances in medicine and medical sciences are indispensable parts of medical literature; they bridge the gap between journal articles, which are timely but usually narrow in scope, and the monograph or textbook with its broad view but infrequent revision.

The *Annual Review of Medicine*, now appearing in its twelfth volume, fills this gap very well. "Medicine" is used here to mean all of medicine and not simply the special province of internists. This volume, for example, includes a review of psychometrics, one on the physiology of the placenta, and a review of hormonal influences on renal function which is aimed more at the renal physiologist than at the clinician. Nevertheless, two-thirds of this volume will be valuable to internists.

Reviews of the respiratory viruses and of side reactions to antimicrobial agents will attract clinicians with a special interest in infectious disease. Gastroenterologists will be able to use reviews of the physiology of the surgically-altered stomach, of recent studies in celiac sprue, and of bile pigment metabolism. The last of these three, by Klatzkin, is the longest in this volume and must be one of the most comprehensive, on this topic, to appear in recent years.

Other metabolic material includes an evaluation of oral hypoglycemic agents by Alexander Marble, a review of iron metabolism by Beutler who gives special emphasis to the diagnosis of iron deficiency, and a summary of porphyrin metabolism and clinical syndromes of porphyria by Eales.

Clinical problems are also central concerns of Robin's review of the myocardiopathies, Relman and Levinsky's discussion of acquired renal tubular defects (especially those of water handling and of acid-base regulation), and Gaensler's critical comments on methods for evaluating pulmonary function.

Exhaustive indices to authors cited in the reviews and to subject matter appear, as in previous volumes; in addition, the titles of the reviews in Volumes 8 to 12 are grouped in a separate index under main headings.

This twelfth volume of the *Annual Review of Medicine* holds to the high standards of completeness and the critical view it has followed in the past.

EDWARD J. HUTH, M.D.

The Relief of Symptoms. 2d Ed. By WALTER MODELL, M.D., F.A.C.P. 374 pages; 24.6 × 18 cm. The C. V. Mosby Company, St. Louis, 1961. Price, \$11.50.

In this second edition, the author has provided for the medical student and beginning physician the practical treatment of twenty-seven of the most common symptoms in an organized, easily read form. These discussions are based not only upon many years of clinical practice but also upon the experience of the author in clinical evaluation of drugs. Theoretical aspects of the relief of symptoms are examined in the first three chapters, and in the fourth, essential factors to be considered in the use of any drug, including placebo, are set forth. The chapters on treatment of various types of pain as well as those on edema, insomnia, and anxiety are particularly to be commended.

The goal and evaluation of drug therapy are delineated for each symptom discussed and the effectiveness and limitations of drug theory considered. Attention is paid to the factors of the individual patient, hospitalized or ambulant, as well as the influence of these factors on desired drug action. Throughout the book newer agents are evaluated in comparison with older, established drugs. Toxic effects of both new and older agents are given the emphasis they deserve. In instances where many agents are available, tables containing both nonproprietary and proprietary names are given. Additional references and an index are included.

While some may disagree with certain statements which are based on personal preference, the older physician might well use Dr. Modell's book to review his approach to the use of drugs and their toxic actions. It appears that the most valuable aspect of this book is the setting forth of the principles of drug therapy which are valid not only for current drugs, but also for agents that will be developed in the future.

N. H. VINCENT, PH.D.

Drugs in the Treatment of Disease. Specifically Commissioned Articles from the British Medical Journal. Preface by HUGH CLEGG. 516 pages; 22 × 14.5 cm. B. M. A. House, Tavistock Square, London, 1961. Price, 35 s.

Regularly, the *British Medical Journal* publishes short, succinct, and explicit articles on the treatment of diseases with drugs. Many of these articles, which were first published between 1958

and 1960 in that journal, have been rewritten by the original authors, presumably to reflect latest opinions, and gathered into this volume.

Some chapters are devoted to groups of drugs, such as the chlorpromazine group, the antihistamines, the antacids, and the diuretics, while others are based on treatment of disease entities and symptom states, such as insomnia, gout, and thyrotoxicosis. The points of view expressed are sound; they show healthy skepticism toward the proliferation of drugs in the same genera, of variants promoted more for commercial advantage than for greater efficacy.

Official drug names cited are British, but this usage is no barrier to understanding of this book by Americans; only rarely do these names differ across the Atlantic. Metric doses are given in most chapters. In the few using apothecary units, the metric equivalents are also given.

This guide to therapy is recommended to any physician who needs authoritative advice on the best present use of drugs. The treatment of uncommon diseases and the use of some drugs with only tentative status (such as those in the anti-neoplasia group) are not presented; these essays cover the most frequent treatable problems of internal medicine, neurology, and dermatology.

EDWARD J. HUTH, M.D.

Mayo Clinic Diet Manual. 3rd Ed. By the COMMITTEE ON DIETETICS OF THE MAYO CLINIC. 222 pages; 23.5 × 16.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$5.50.

The most commonly needed diets for therapy and diagnosis are set forth clearly in this new edition of the *Mayo Clinic Diet Manual*. Gluten-restricted diets, invaluable in the treatment of celiac disease and idiopathic steatorrhea, are given their due weight and detail. The increasing use of "normal" calcium diets for the assessment of urinary calcium excretion is reflected by the inclusion of a 700 milligram calcium diet; most Americans ingest more calcium than this in their daily food, but the difference in urinary calcium excretion between that found with an intake of 700 milligrams and of 900 milligrams is a quibbling amount.

Diets of very unusual application, such as a low urinary solute diet for nephrogenic diabetes insipidus, a diet for phenylketonuria, have not been included.

An Appendix listing valuable supplementary data includes caloric values of beverages,

acidity-alkalinity values for foods, foods high in potassium, height-weight-age tables, and a nomogram for estimation of basal calorie needs and ideal weight.

EDWARD J. HUTH, M.D.

The Merck Manual. 10th Ed. CHARLES E. LYGHT, M.D., Editor. 1,907 pages; 17.5 × 11 cm. Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey, 1961. Price, \$7.50 (regular edition); \$9.75 (deluxe edition).

This is the tenth edition of this familiar and popular book since 1899 and it does credit to its predecessors. Designed to provide the physician with a ready source of information, *The Merck Manual* admirably fulfills its function.

The present edition of about 1,900 pages is divided into two main sections. Part I includes the diagnostic and therapeutic material and Part II is a manual of clinical procedures, laboratory tests, radioisotopes, and immunization methods.

The clinical section contains twenty-one chapters on each of the specialized fields of medicine from allergy to venereal diseases, and embraces a wide variety of disorders. The discussions are brief and to the point, accurate and usually up to date. An exception to the latter is the omission of chromosomal abnormalities, although a well-written section on genetic metabolic disturbances is included. External cardiac massage is omitted from the discussion of cardiac standstill.

Each entity is described from an etiological, physiological, and pathological standpoint. The chapter on physical and chemical agents is particularly well done and includes an outstanding section on poisoning. The text is liberally sprinkled with illustrations and tables that are clear and concise.

Included in Part I is a chapter on therapy. Prescriptions have been streamlined and modernized. Relatively few good old-fashioned compound prescriptions remain. The metric system and generic nomenclature are used throughout. This section contains well-written descriptions of the use of anticoagulants, thrombolytic agents, diuretics, steroids, antibiotics, and psychopharmacologic drugs.

Part II contains detailed descriptions of bedside procedures that the practicing physician

may be called upon to perform or describe. Clinical procedures, immunization schedules, sample diets, and office laboratory procedures are also included in Part II.

The Merck Manual is clearly printed, well indexed, and reasonably priced. It has retained its familiar and convenient compact format. If one is wearing a coat, *The Merck Manual* may still be considered "pocket-sized."

RALPH MYERSON, M.D.

Hypokinetic Disease. By HANS KRAUS, M.D., and WILHELM RAAB, M.D., F.A.C.P., F.A.C.C., F.C.C.P., F.A.C.S.M. 193 pages. 23.5 × 16 cm. Charles C Thomas, Springfield, 1961. Price, \$7.50.

With a concern over the lack of exercises performed by the average person in the United States, Drs. Kraus and Raab have developed the thesis that specific diseases may be produced, or, in any event, made significantly worse, by this "under-exercise." The conditions stressed in this book are back pains, cardiac problems, obesity, and emotional instability. Anyone agreeing with their premise will find much corroborating evidence and a stimulating treatise. Even where the conclusions are based upon empirical data, one cannot help being impressed with the importance of adequate regular exercising for its therapeutic and prophylactic results.

Interest in this area has been stimulated by commissions appointed by Presidents from both political parties within recent years. Adequate references are made to these. This book carries an *Introduction* by Howard A. Rusk, M.D., F.A.C.P., and a *Foreword* by Paul D. White, M.D., F.A.C.P. The section on the differences between the athlete's heart and the loafer's heart and the physiology and effects of exercise upon cardiac rehabilitation should be of distinct value to the cardiologist. The book is recommended to those interested in cardiac rehabilitation and the prevention of musculo-skeletal problems, particularly back aches.

All physicians would do well to heed the recommendations in their personal lives as well as to follow them in the management of patients. There are adequate illustrations and diagrams and the book is easy to read.

WILLIAM J. ERDMAN, II, M.D.

Book Notices

Neurophysiology. By THEODORE C. RUCH, PH.D., HARRY D. PATTON, PH.D., M.D., J. WALTER WOODBURY, PH.D., and ARNOLD L. TOWE, PH.D. 521 pages; 26 × 17 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$10.00.

Twenty-two chapters from the Ruch-Fulton textbook of physiology, *Medical Physiology and Biophysics*, have been reprinted in this volume. The topics covered are biophysics of the cell membrane, nerve and muscle physiology, the motor and sensory functions of the nervous system, and the neurophysiology of the cerebral cortex and behavior. The volume stands independently of its source, through the preparation of an index referring only to these reprinted chapters.

This format should meet the needs of neurologists who wish to have a good current resumé of neurophysiology but do not wish to pay the cost of a complete textbook of physiology. Cardiologists may find the first two chapters to be very useful in gaining a picture of present views of the relations of ion transport and movement to cell membrane potentials.

EDWARD J. HUTH, M.D.

Famous Faces in Diabetes. Compiled by CECIL STRIKER, M.D., with a foreword by ELLIOTT P. JOSLIN, M.D. 256 pages; 26 × 18 cm. G. K. Hall & Company, Boston, 1961. Price, \$25.00.

We took sweet counsel together.
—Psalms 55:14

Here is an array of physicians, chemists, and physiologists who have studied diabetes mellitus and cared for its victims. The lineage

runs from the Indian, Susruta ("The urine looks like honey and acquires a sweet taste,"), ca. 1,000 B.C., to our contemporaries. For each illustration a brief note describes the pertinence of this man or animal or place to the history of diabetes mellitus.

Most of the illustrations are of adequate quality but some (e.g., reproductions from Garrison's *History of Medicine*, and the picture of the first dog to have had pancreatectomy and survive after insulin therapy) are poor.

A bibliography of sources for the historical notes and person and subject indices are at the end of the book.

EDWARD J. HUTH, M.D.

The Stages of Human Development before Birth. By E. BLECHSCHMIDT, M.D. 684 pages; 27 × 20 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$23.00.

Dr. Blechschmidt's presentation of human embryology uses the atlas form. Right-hand pages illustrate the development of the embryonic and fetal body and that of particular regions with drawings, photomicrographs, and photographs of generous size; left-hand pages carry text (German and English in parallel columns) and the keys to the illustrations in German with English translations in brackets. An index in English follows the German index.

The typography and printing are of fine quality although a few plates apparently produced from halftones in previous publications lack good definition.

EDWARD J. HUTH, M.D.

Books Recently Received

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be selected for review, but it is not possible to discuss all of them.

Bulletin of the World Health Organization. Communicable Diseases. Influenza, Arthropod-Borne Diseases, Staphylococcus-Poliomyelitis, Tuberculosis-Leptospirosis. Vol. 24, No. 6. 818 pages; 24 × 18 cm. World Health Organization, Geneva, 1961. Price, \$2.00.

Cancer Prognosis Manual. By ARTHUR G. JAMES, M.D., F.A.C.S. 74 pages; 27.5 × 21.5 cm. American Cancer Society, Inc., New York, 1961.

Ciba Foundation Study Group. No. 8. Problems of Pulmonary Circulation. A. V. S. DE REUCK, M.Sc., D.I.C., A.R.C.S., and MAEVE O'CONNOR, B.A., editors for the Ciba Foundation. 96 pages; 19 × 13 cm. Little, Brown and Company, Boston, 1961. Price, \$2.50.

Every-Day Prescriptions with Hints on Treatment. 2d Ed. By PRANKUMAR GUHA, M.B., I.M.S. (Retd.) 397 pages; 16.5 × 11 cm. P. Guha, 8A, Pasupatinath Bose Lane, Bagh-bazar, Calcutta 3, India, 1960. Price, 6 rupees.

Handbook on Clinical Electromyography. By ROBERT B. PEARSON, M.D. 72 pages; 21.5 × 14 cm. The Meditron Company, El Monte, California, 1961.

Mayo Clinic Diet Manual. 3d Ed. By the COMMITTEE ON DIETETICS OF THE MAYO CLINIC. 222 pages; 23.5 × 16.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$5.50.

The Nature of Sleep. Ciba Foundation Symposium. G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and MAEVE O'CONNOR, B.A., editors for the Ciba Foundation. 416 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1961. Price, \$10.00.

Opere Alese: Vol. IV. Hipofiză, Epifiză, Suprarenală, Pancreas, Ovar și Testicul. By C. I. PARHON. 637 pages; 24.5 × 17.5 cm. Editura Academiei Republicii Populare Române, Bucharest, 1961.

The Physician in Industry. By WILLIAM P. SHEPARD, M.D., M.A. 290 pages; 22 × 14.5 cm. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1961. Price, \$9.50.

Physiology of the Digestive Tract. By HORACE W. DAVENPORT, PH.D., D.Sc. (Oxon.) 221 pages; 26 × 18.5 cm. Year Book Medical Publishers, Inc., Chicago, 1961. Price, \$8.50.

Poliomyelitis. Papers and Discussions Presented at the Fifth International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. 435 pages; 26 × 18 cm. Medical Department, J. B. Lippincott Company, Philadelphia, 1961. Price, \$7.50.

The Practical Management of Head Injuries. By JOHN M. POTTER, M.A., M.B., B.C.H.I.R. (Cantab.), F.R.C.S. 84 pages; 18.5 × 12.5 cm. Year Book Medical Publishers, Inc., Chicago, 1961. Price, \$2.50.

Problems of Hereditary Chondrodysplasias. A Roentgenological, Clinical and Genetic Study of 70 Cases of Hereditary Chondrodysplasias in 42 Norwegian Families. Norwegian Monographs on Medical Science. By ANDREAS HOBAEK, M.D. 175 pages; 24.5 × 18 cm. Oslo University Press, Oslo, 1961. Price, \$7.50.

Proceedings of the Thirteenth International Congress on Occupational Health, Held July 25–29, 1960. Compiled by L. WADE, M.D., and others comprising the Executive Committee of the Thirteenth International Congress on Occupational Health. 1,005 pages; 27 × 18.5 cm. Book Craftsmen Associates, Inc., New York, 1961.

Public Health Papers No. 8. The Role of Immunization in Communicable Disease Control. Available through Columbia University Press, International Documents Service, New York 27. 118 pages; 21.5 × 14 cm. World Health Organization, Geneva, 1961. Price, \$1.25.

Public Health Papers No. 9. Teaching of Psychiatry and Mental Health. Available through Columbia University Press, International Documents Service, New York 27. 186 pages; 21.5 × 14 cm. World Health Organization, Geneva, 1961. Price, \$2.00.

Public Health Papers No. 10. Control of Soil-Transmitted Helminths. By PAUL C. BEAVER. Available through Columbia University Press, International Documents Service, New York 27. 44 pages; 21.5 × 14 cm. World

Health Organization, Geneva, 1961. Price, \$60.

Report of the Committee on the Control of Infectious Diseases, 1961 Ed. ALEX J. STEIGMAN, M.D., Chairman. 132 pages; 23 × 15.5 cm. American Academy of Pediatrics, Evanston, Ill., 1961. Price, \$1.00. (paper bound.)

Report of the Medical Research Council for the Year 1959-1960. By the COMMITTEE OF PRIVY COUNCIL FOR MEDICAL RESEARCH. 326 pages, 24.5 × 15 cm. Her Majesty's Stationery Office, London, 1961. Price, 15s. 6d.

Samson Wright's Applied Physiology. 10th Ed. Revised by CYRIL A. KEELE and ERIC NEIL, with the collaboration of JOHN B. JEPSON. 555 pages; 28.5 × 23 cm. Oxford University Press, New York, 1961. Price, \$13.50.

Starling's Law of the Heart. By LOE PING KIAN, M.D. 88 pages; 24 × 16 cm. Keng Po, Djakarta, Indonesia, 1961.

Sterility. Office Management of the Infertile Couple. Edited by EDWARD T. TYLER, M.D. 425 pages; 20.5 × 14.3 cm. The Blakiston Division of McGraw-Hill Book Company, Inc., New York, 1961. Price, \$12.50.

Symptom Diagnosis. 5th Ed. By WALLACE MASON YATER, A.B., M.D., M.S.(MED), F.A.C.P., and WILLIAM FRANCIS OLIVER, B.S., M.D., F.A.C.P. 1,035 pages; 25 × 17 cm. Appleton-Century-Crofts, Inc., New York, 1961. Price, \$15.00.

Transactions of the American Society for Artificial Internal Organs. Vol. VII. GEORGE E. SCHREINER, M.D., editor. 391 pages; 28 × 24 cm. Georgetown University Printing Department, 1961. Copies may be ordered from

George E. Schreiner, M.D., Department of Medicine, Georgetown University Hospital, Washington 7, D. C. Price, \$8.00.

World Health Organization Technical Report Series No. 209. The Teaching of the Basic Medical Sciences in the Light of Modern Medicine. Eighth Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. Available through Columbia University Press, International Documents Service, New York 27. 31 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Price, \$.30 (paper bound).

World Health Organization Technical Report Series No. 216. Recommended Requirements for Schools of Public Health. Available through Columbia University Press, International Documents Service, New York 27. 24 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Price, \$.30 (paper bound).

World Health Organization Technical Report Series No. 220. Evaluation of the Carcinogenic Hazards of Food Additives. Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives. Available through Columbia University Press, International Documents Service, New York 27. 36 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Price, \$.60.

World Health Organization Technical Report Series No. 221. Scientific Meeting on Rehabilitation in Leprosy. Available through Columbia University Press, International Documents Service, New York 27. 37 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Price, \$.60.

MEDICAL NEWS

MEETINGS

- Dec. 2-7. AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILIOLOGY, Palmer House, Chicago. Dr. Robert R. Kierland, Mayo Clinic, Rochester, Minn., Secretary-Treasurer.
- Jan. 18-20, 1962. AMERICAN SOCIETY OF CLINICAL RADIOLOGY, Arizona Biltmore Hotel, Phoenix, Arizona. Louis Shattuck Baer, M.D., 411 Primrose Road, Burlingame, California, Secretary.
- April 9-13. AMERICAN COLLEGE OF PHYSICIANS, Bellevue-Stratford Hotel, Philadelphia. Edward C. Rosenow, Jr., M.D., 4200 Pine St., Philadelphia 4, Executive Director.
- April 28. AMERICAN SOCIETY FOR CLINICAL NUTRITION, Chalfonte Hotel, Atlantic City, New Jersey, Robert E. Hodges, M.D., Secretary-Treasurer.
- April 30-May 2. AMERICAN ACADEMY OF PEDIATRICS, Statler-Hilton Hotel, New York City. E. H. Christoperson, M.D., 1801 Hinman Ave., Evanston, Ill., Executive Director.
- June 21-25. AMERICAN COLLEGE OF CHEST PHYSICIANS, 28th Annual Meeting, Morrison Hotel, Chicago, Illinois. Mr. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois, Executive Director.

INTERNATIONAL AND FOREIGN MEETINGS

- Jan. 22-24, 1962. FIRST INTER-AMERICAN CONFERENCE ON CONGENITAL DEFECTS, The Statler Hotel, Los Angeles. Stanley E. Henwood, Executive Secretary, International Medical Congress Ltd., Room 3013, 120 Broadway, New York 5.
- Feb. 20-24. SEVENTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, New Delhi, India. Mr. Murray Kornfeld, Executive Director, 112 East Chestnut Street, Chicago 11, Ill.
- Mar. 26-31. HEALTH AND TUBERCULOSIS CONFERENCE, University College, Ibadan, Nigeria. Conference Secretary, The Chest and Heart Association, Tavistock House North, Tavistock Square, London, W. C. 1.
- April 23-25. EIGHTH PAN-AMERICAN CONGRESS OF GASTROENTEROLOGY, Hotel Roosevelt, New York. Charles A. Flood, M.D., Executive Secretary.

POSTGRADUATE COURSES

THE AMERICAN COLLEGE OF PHYSICIANS

Schedule of Postgraduate Courses, Fall-Winter, 1961-62

- COURSE NO. 4, ADVANCES IN ELECTROCARDIOGRAPHY, New York University Medical Center, New York, N. Y.: Charles E. Kossmann, M.D., F.A.C.P., Director; December 4-8, 1961.
- COURSE NO. 5, INTERNAL MEDICINE—TODAY'S PROBLEMS IN DIAGNOSIS AND MANAGEMENT, AND TOMORROW'S PROJECTIONS, Ochsner Foundation Hospital, New Orleans, La.; A. Seldon Mann, M.D., F.A.C.P., and William D. Davis, Jr., M.D., F.A.C.P., Co-Directors; January 15-18, 1962.
- COURSE NO. 6, MEDICAL GENETICS, The University of Michigan Medical School, Ann Arbor, Mich.; James V. Neel, M.D., F.A.C.P., Director; January 29-February 1, 1962.
- COURSE NO. 7, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS, Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., F.A.C.P., and Edward H. Reinhard, M.D., F.A.C.P., Co-Directors; February 12-16, 1962.
- COURSE NO. 8, SYMPOSIA ON CHALLENGING MEDICAL PROBLEMS, Baylor University College of Medicine, Houston, Tex.; Raymond D. Pruitt, M.D., F.A.C.P., Director; February 19-23, 1962.
- For information and application blanks, please write directly to Edward C. Rosenow, Jr., M.D., Executive Director, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.
- AMERICAN COLLEGE OF CARDIOLOGY**
- DEC. 5-8. WORKSHOP IN CARDIOLOGY, Institute for Cardiopulmonary Diseases of the Scripps Clinic and Research Foundation, La Jolla, California. Tuition, \$50.00 for members and fellows of the American College of Cardiology, \$100.00 for other physicians. Residents and interns admitted without charge. Advance enrollment required. For information write Philip Reichert, M.D., Executive Director, American College of Cardiology, Empire State Building, New York 1.

CENTER FOR CONTINUATION STUDY, UNIVERSITY OF MINNESOTA—MEDICAL CONTINUATION COURSES

Jan. 2-6, 1962. **INTERMEDIATE ELECTROCARDIOGRAPHY FOR GENERAL PHYSICIANS AND SPECIALISTS.** For further information write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

AMERICAN DIABETES ASSOCIATION

Jan. 17-19, 1962. **TENTH POSTGRADUATE COURSE, "DIABETES IN REVIEW: CLINICAL CONFERENCE, 1962."** Sessions of the first and third days will be at The Statler Hilton, Detroit; those of the second day will be at the University of Michigan, Ann Arbor. The American Academy of General Practice will give 19 hours of Category II credit for the course. Registration is open to Doctors of Medicine; the fee is \$40.00 for members of the American Diabetes Association, and \$75.00 for non-members. Additional data and registration forms may be secured from American Diabetes Association, 1 East 45th Street, New York 17.

TEMPLE UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL

Mar. 5-16, 1962. **POSTGRADUATE COURSE IN ALLERGY.** A continuous two-week course offered by the Departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania. Sessions will be held daily at the Temple University Medical Center from 9:00 AM to 5:00 PM. Tuition, \$175.00; enrollment limited. Louis Tuft, M.D., is course director; George I. Blumstein, M.D., and Merle M. Miller, M.D., are associate directors. For brochure and application forms write to George Blumstein, M.D., Temple Medical Center, Philadelphia 40.

EXAMINATIONS AND LICENSURE

AMERICAN BOARD OF PEDIATRICS: Written: Jan. 12, 1962. Oral: Atlantic City, April 28-May 1; San Francisco, June 15-18; Chicago, Oct. 6-8; and Pittsburgh, Nov. 30-Dec. 3. Final date for filing application for the written examination is November 30, 1961. Dr. John McK. Mitchell, Rosemont, Pa., Secretary.

AMERICAN BOARD OF PREVENTIVE MEDICINE: Written examination in public health, avia-

tion medicine, and occupational medicine, spring of 1962. Dr. Tom F. Whayne, 4219 Chester Ave., Phila. 4, Pa., Secretary.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Chicago, Oct. 9-10, 1961, and New York, Dec. 11-12. David A. Boyd, Jr., 102-110 Second Ave., S. W., Rochester, Minn., Secretary.

AMERICAN BOARD OF INTERNAL MEDICINE

I. **Written Examination—October 15, 1962.** The closing date for acceptance of applications—May 1, 1962.

II. **Oral Examinations:** New Orleans—January 28, February 1, 1962. The closing date for acceptance of applications—December 15, 1961.

Philadelphia—April 3-7, 1962. The closing date for acceptance of applications—January 2, 1962.

San Francisco—September 9-13, 1962. The closing date for acceptance of applications—April 1, 1962.

Chicago—November 4-8, 1962. The closing date for acceptance of applications—April 1, 1962.

Subspecialty oral examinations in Gastroenterology:

Ann Arbor, Michigan—March 26-27, 1962. The closing date for acceptance of applications—February 1, 1962.

AMERICAN BOARD OF NUTRITION

The American Board of Nutrition will hold the next examination for certification as Specialist in Human Nutrition on Sunday, April 8, 1962, in Atlantic City, New Jersey. Candidates who wish to be considered for this examination should forward applications to the Secretary's office not later than March 1. Application forms may be obtained from the Secretary, Robert E. Shank, M.D., Department of Preventive Medicine, Washington University School of Medicine, Euclid and Kingshighway, St. Louis 10, Missouri.

COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS

March 12-14, 1962. A symposium, "Basic Problems in Neoplastic Disease," will commemorate the fiftieth anniversary of the Institute of Cancer Research at Columbia University and the tenth anniversary of its affiliated clinical facility, The Francis Delafield Hospital. The symposium is open without fee

to all interested workers in this field. For details and applications, write to the Institute for Cancer Research, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York 32, N. Y.

AMERICAN PSYCHOSOMATIC SOCIETY

Mar. 30-April 1, 1962. The American Psychosomatic Society will hold its nineteenth annual meeting at The Sheraton Hotel, Rochester, N. Y. The program committee welcomes abstracts of original work to be presented at the meeting by members or non-members. Abstracts should be not more than two typewritten pages, and should be submitted in eleven copies. Deadline for submission is December 1, 1961. Abstracts should be addressed to the Chairman, 265 Nassau Road, Roosevelt, N. Y.

THREE-YEAR RESIDENCY IN NEOPLASTIC DISEASES

The Francis Delafield Hospital, affiliated with Columbia University College of Physicians and Surgeons, New York, offers a three-year residency program accredited by the American Board of Internal Medicine.

The first year includes general medicine consisting of ward service, hematology, cardiology, and diagnostic radiology. The second year includes training in either hematology or cardiology, and supervision of first year residents. The third year may be served as the chief resident or in a fellowship program. Opportunity to do clinical and laboratory investigations is available during the second and third years.

The program can be started July 1, 1962. The stipend depends upon individual experience, minimum, \$3,380, and living quarters are provided in the hospital. Applications should be addressed to Alfred Gellhorn, M.D., Director of Medicine, Francis Delafield Hospital, 99 Fort Washington Ave., New York 32, N. Y.

YOUNG INVESTIGATORS AWARD FOR 1962

The American College of Cardiology offers a Young Investigators Award of a silver medal and \$1,000.00, in addition to one honorable mention award and \$250.00, and eight awards of \$100.00 each. Any physician in residence or fellowship status, or within three years following this residence or fellowship, is eligible to participate with a formal presentation, ten min-

utes in length, describing original investigation, placed in competition, before the eleventh annual meeting of the American College of Cardiology, in Denver, Colorado, May 29 to June 2, 1962. An original manuscript and letter indicating intention to enter competition must be accompanied by a letter from the chief of the service or laboratory indicating his willingness to have the material placed in the competition. Address queries and manuscripts to Executive Director, American College of Cardiology, Empire State Building, 350 Fifth Avenue, New York 1.

THE VAN METER PRIZE AWARD FOR 1962

The American Thyroid Association, Inc., again offers the Van Meter prize award of \$500.00 to the essayist submitting the best manuscript of original and unpublished work concerning "Goiter—especially its basic cause." The studies may relate to any aspect of the thyroid gland in all of its functions in health and disease. The award will be made at the annual meeting of the association at the Roosevelt Hotel, New Orleans, Louisiana, May 9-12, 1962. A place on the program will be reserved for the winning essayist if he can attend the meeting. When more than one author's name appear on the manuscript the authors will be asked to designate a single recipient to receive the award.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length, and must be presented in English. Duplicate, typewritten copies, double spaced, should be sent to the Secretary, Theodore Winship, M.D., 430 N. Michigan Ave., Chicago 11, Illinois, not later than January 1, 1962.

NEW ENGLAND CENTER HOSPITAL

A graduate training program in cardiology is announced by the New England Center Hospital, Boston, Massachusetts. The three-year program will combine didactic training in science at the Massachusetts Institute of Technology with experience in laboratory and clinical research and clinical cardiology at the hospital. Tuition fees and stipends will be provided through a grant from the National Heart Institute. Further information may be obtained from M. S. Raben, M.D., New England Center Hospital, 171 Harrison Avenue, Boston 11, Massachusetts.

INSTRUCTIONS TO AUTHORS

MANUSCRIPTS: All papers should be typewritten on one side of the paper and double spaced (including references, figure legends, and footnotes). The original and one carbon copy should be submitted with duplicate copies of all figures and tables. A separate title page should include the following: title, subtitle (if any), author(s) and his (their) degree(s), F.A.C.P. (if Fellow of the American College of Physicians), city or town where the work was done, hospital or academic institution (if any), and necessary acknowledgment of financial sponsors.

The introduction should orient the paper in relation to its field and should state its purpose. The main sections (for example, RESULTS) should be identified by centered headings in capital letters. Indicate further subdivisions by side headings that are flush with the left-hand margin and one line above the text, and/or by paragraph headings which should be indented on the first line of the paragraph and underlined. Extensive discussion should be separated from the presentation of the results. A succinct summary should state what was done, what was found, and what the findings are interpreted to mean. For guidance to sound grammar and clear style consult *The Elements of Style* by W. Strunk, Jr. and E. B. White, The Macmillan Co., New York, 1959.

ABBREVIATIONS, SYMBOLS, AND NOMENCLATURE: Abbreviations should conform as closely as possible to the *Style Manual for Biological Journals*, published in 1960 by the Conference of Biological Editors, Committee on Form and Style, American Institute of Biological Sciences, 2000 P Street, NW, Washington 6, D. C. Abbreviations should be kept to a minimum, should be defined when first used, and should be redefined in the summary; the forms of some frequently used abbreviations are listed at the bottom of this page. Generic names of drugs are preferred; a proprietary name may be given following the first use of the generic name. *Webster's New International Dictionary* is the standard reference for spelling, compounding, and hyphenating. Cardiopulmonary nomenclature is used as given in "Standardization of definitions and symbols in respiratory physiology," *Fed. Proc.* 9: 602, 1950.

REFERENCES: These are to be cited consecutively in the text as numbers enclosed in parentheses *on the line of writing*, not as superscript numbers. At the end of each article references should be listed *in the numerical order in which they are first cited in the text*. This list should conform to the style of the *Index Medicus* but with end pagination and number and month of issue omitted, and should be punctuated as in the following examples.

For journal articles: Surname and initials of author(s) (in capitals), title of article (lower case), name of journal (underlined for italics), volume number, first page, year. Thus:

4. DOE, J. E., ROE, R. C.: What I know about it. *Ann. Intern. Med.* 27: 1590, 1960.

TO AUTHORS

For books: Surname and initials of author(s) (in capitals), title and subtitle (caps and lower case, underlined for italics), edition (other than first), publishing house, city, year, page or chapter as specific reference. Thus:

5. OSLER, W.: *Aequanimitas. With Other Addresses to Medical Students, Nurses and Practitioners of Medicine*, 3rd Ed., H. K. Lewis and Co., London, 1948, p. 250.

For articles in books: Surname and initials of author(s) (in caps), title of article (lower case), chapter number (if any), first page of article, title of book (caps and lower case, underlined for italics), editor, edition (other than first), publishing house, city, year. Thus:

6. WINTERNITZ, M. C.: Notes on an attack of coronary artery disease, in *When Doctors are Patients*, ed. by Pinner, M. and Miller, B. F., W. W. Norton and Co., New York, 1952, p. 31.

References to articles in press must state name of journal and, if possible, volume and year.

Authors are responsible for bibliographic accuracy; authors must check every reference in manuscript and *again* in galley-proof.

FOOTNOTES: Footnotes to tables should be designated by symbols in the following order: *, †, ‡, §, ||, #, **, ††, ‡‡, etc. Footnotes to the text should be as few as possible and should be typed at the foot of the appropriate page separated from the text by a ruled line.

TABLES: These should be typed on separate sheets with number and title (in caps) and centered. Symbols for units should be confined to the column headings. Vertical lines should be omitted. All data should be checked for accuracy.

FIGURES: These should be submitted in photographic form (glossy prints) or as original india ink drawings if no larger than standard page; poor freehand lettering is not acceptable. Prints should not be mounted, stapled, or clipped. They should be labeled on back (lightly in pencil) with name(s) of author(s) and figure number, and the top indicated. Legends should be typed consecutively on a separate sheet. In photographs, identities of patients should be masked. In case of prior publication the author must obtain permission from the previous author and copyright holder to reproduce the figure in the ANNALS. Six illustrations are allowed without cost; above this number the actual cost is charged to the author.

ABSTRACTS: Each paper must be accompanied by an abstract typed in double space and in triplicate (for translation into Interlingua, for *Biological Abstracts*, and for the abstracting service of the J. A. M. A.). Title and authors should be given followed by a concise statement in not more than 250 words of (1) what was done, (2) what was found, and (3) what was concluded.

ABBREVIATIONS

intramuscular	im	centigrade	C	millimeter	mm	volume	vol
intraperitoneal	ip	Fahrenheit	F	centimeter	cm	milliliter	ml
intravenous	iv	specific gravity	sp gr	meter	m	liter	liter
subcutaneous	sc	hemoglobin	Hb	cubic millimeter	mm ³	concentration	conc
by mouth	po	pressure of CO ₂	P _{CO₂}	square meter	m ²	microequivalent	μEq
min, lethal dose	MLD	number	no.	weight	wt	milliequivalent	mEq
unit	U	standard deviation	sd	microgram	μg	millimolar	mM
international unit	IU	standard error	se	milligram	mg	milliosmole	mOsm
minute	min	probability	P	gram	g	milligram per cent	
calorie (small)	cal	correlation coefficient	R	kilogram	kg	mg per 100 ml	

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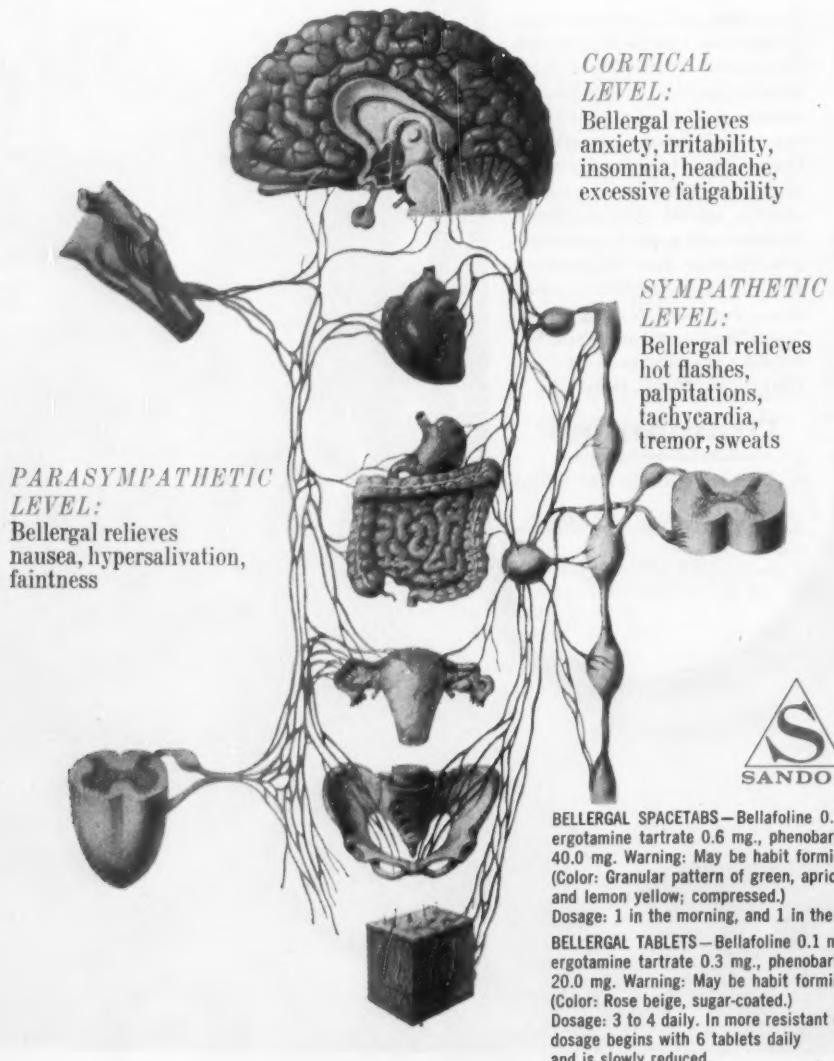
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without serious side effects or habituation During three and one-half years of clinical study in 1,759 patients,²⁻¹³ Listica has produced no serious side effects. Less than 4% of patients experienced any side effects, and these were invariably minor and transient. Most frequent (38 cases) was mild drowsiness, which disappeared after the first few days of Listica therapy. Habituation, cumulative effects, or withdrawal symptoms have not been noted, even in patients taking Listica as long as two years.

with convenient dosage and availability One Listica tablet, q.i.d., is the recommended dosage. Listica is supplied in bottles of 50 tablets on prescription only, by pharmacies everywhere. Each tablet contains 200 mg. of Hydroxyphenamate, Armour.

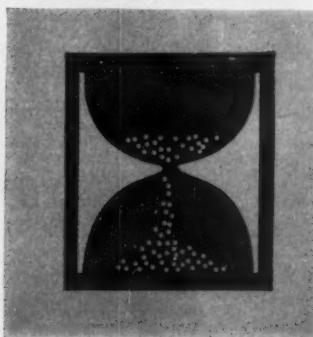
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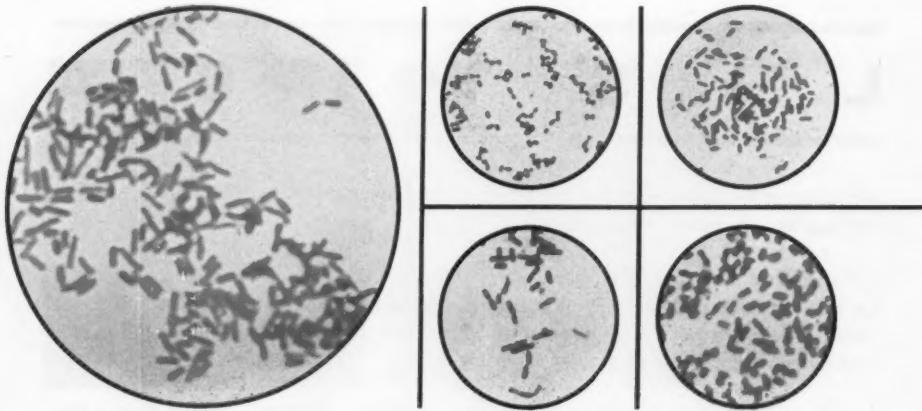


Robert A. Hardt, President

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especially those caused by Pseudomonas*



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FOR EXAMPLE: In one study, Coly-Mycin cleared the urinary tract of *Pseudomonas* infection in 58 of 60 patients. In another study, "Fifteen of the 18 patients infected with *Escherichia coli* who were treated with colistin [Coly-Mycin] had sterile urine cultures upon conclusion of treatment."¹³

PRIMARILY BACTERICIDAL^{1,6,8,10} Unusually effective against a wide range of gram-negative pathogenic bacteria, especially *Pseudomonas aeruginosa*, *Escherichia coli*, *Aerobacter aerogenes* and *Klebsiella pneumoniae*.¹⁻¹⁵ (Not effective against *Proteus*.)

RAPIDLY EFFECTIVE Therapeutic blood levels^{1,6,8,10,11} and urine concentrations are quickly attained.^{5,8}

EXCEPTIONALLY WELL TOLERATED in patients of all ages at recommended dosage. No blood dyscrasia, renal damage, eighth nerve disturbance or other serious reaction has been reported, but minor side effects—such as circumoral paresthesias, pruritus, vertigo, and drug fever—have occurred.

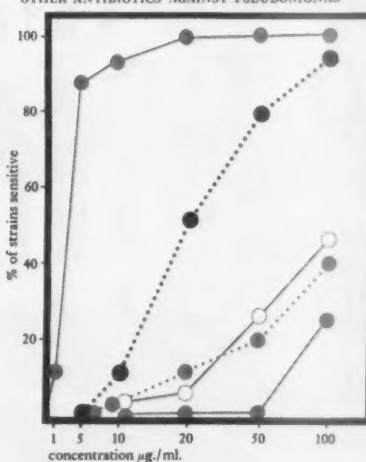
- To date there have been no reports of monilial overgrowth due to Coly-Mycin therapy.
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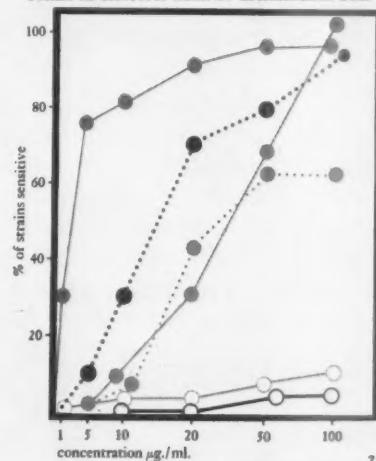
Supplied: In vials containing 150 mg. colistimethate sodium and 8 mg. dibucaine hydrochloride for reconstitution with 2 ml. sterile distilled water for injection. *For intramuscular injection only.*

- References:**
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BACTERICIDAL ACTIVITY OF COLY-MYCIN AND 5 OTHER ANTIBIOTICS AGAINST *ESCHERICHIA COLI**



*Adapted from Petersdorf and Hook.

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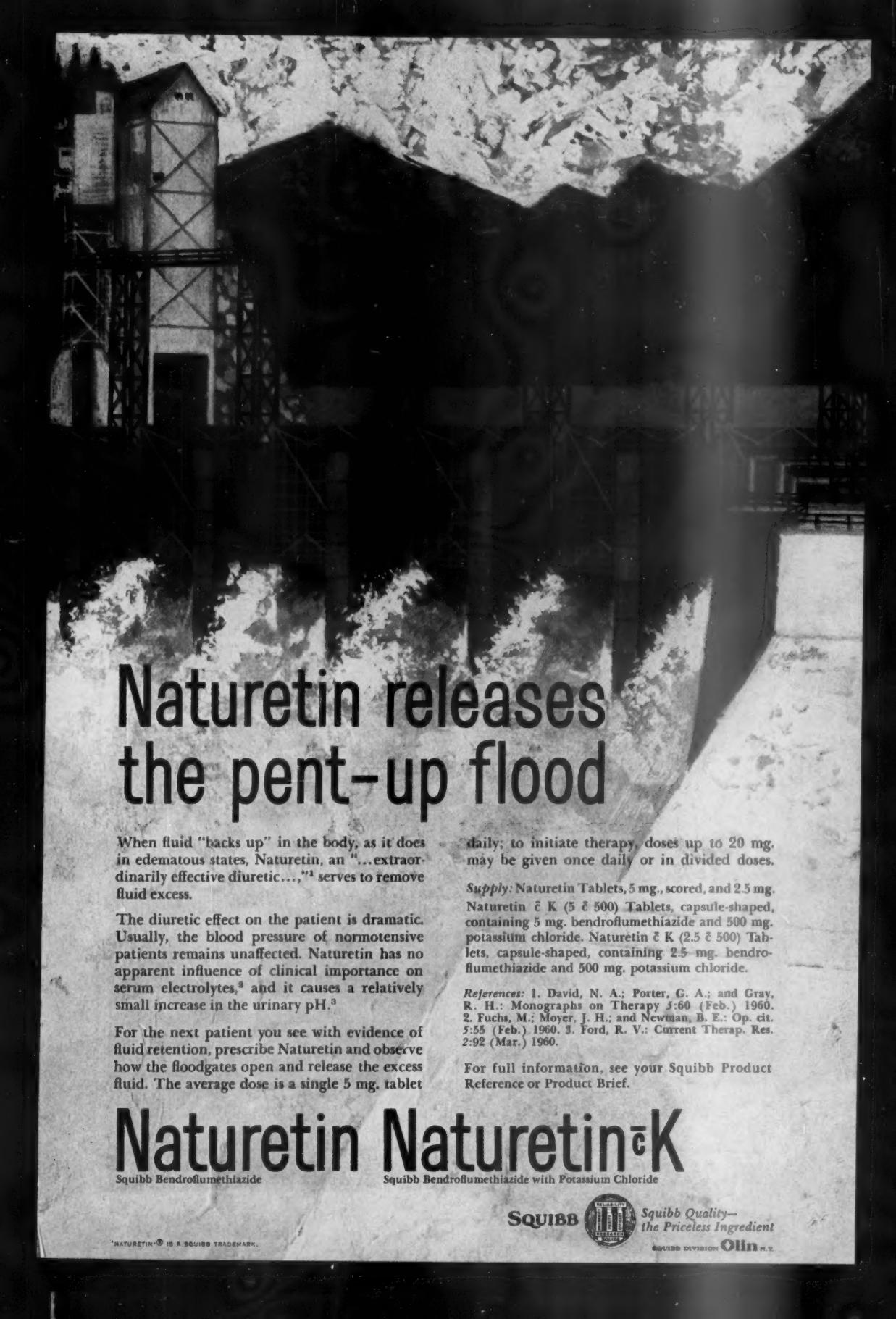
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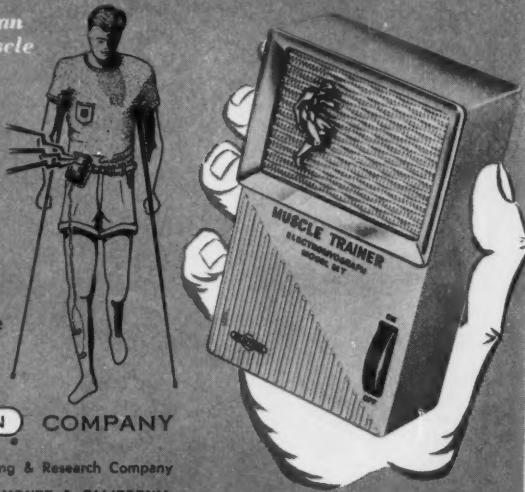
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Terramycin®

BRAND OF OXYTETRACYCLINE

confirmed dependability in fulminating infections is just one reason why



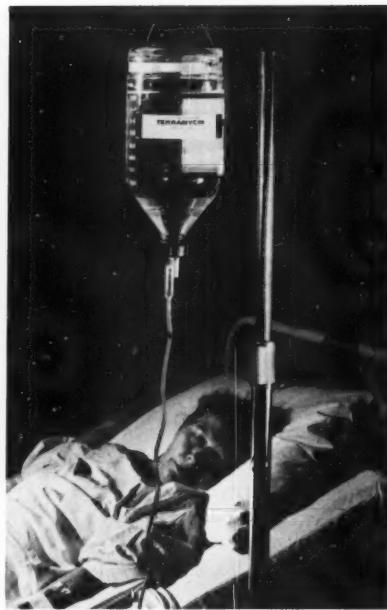
New evidence* demonstrates the effectiveness of Terramycin Intravenous in appendicitis with peritonitis...another reason for the trend to Terramycin.

In a 10-year study, Wenckert and Robertson (Malmo Hospital, Sweden) found that the mortality rate in appendicitis dropped dramatically from 1.17% to 0.22% after Terramycin intravenous therapy was used routinely in those cases with associated peritonitis.

Cases of appendicitis with peritonitis found during the course of 5,564 consecutive appendectomies were treated in the first 5 years with penicillin and/or streptomycin, and those in the latter 5 years with Terramycin administered intravenously and topically. Other procedures involved in the 2 five-year series, except the different antibiotic therapies used, remained essentially the same.

The authors report: "It would, of course, have been of value if the two groups compared had dated from the same period, but in view of the favourable impression soon made by Terramycin, it was not considered justified to deprive alternate patients of the benefit of the agent [Terramycin]."

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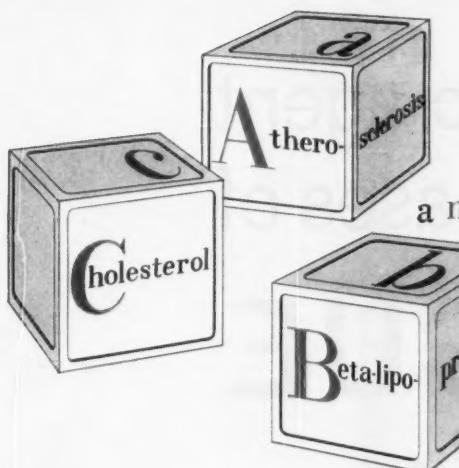
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A recent review of the atherosclerosis problem¹ points out that "cholesterol is only one of the serum lipids which may be related in some way to atherogenesis" and suggests that "specific triglycerides, phospholipids, fatty acids or the whole spectrum of beta-lipoproteins may be of equal or greater importance."

The role of the low-density beta-lipoproteins has been stressed by Olson², who suggests that they are the primary agents in atherosclerosis. Another recent discussion³ has brought out the need for a simple and reliable testing procedure for beta-lipoproteins.

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In addition to its usefulness in atherosclerotic studies, BETA-L TEST may be found a helpful diagnostic and prognostic procedure in diabetes, hypothyroidism, the menopausal state and other conditions associated with elevated beta-lipoproteins.

BETA-L TEST measurements correlate well with total beta (low-density) lipoprotein measurements obtained by electrophoresis⁴ and polyanion precipitation⁴ and with cholesterol values in the beta-lipoproteins⁵.

BETA-L TEST is supplied in 60-test kits.

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General Pharmacological Properties—The IP and PO LD₅₀ values for SPARTASE in rats are 4 and 19 grams/kg., respectively.

The pharmacological activity of aspartic acid has been the subject of numerous publications¹⁻⁸ and need not be reviewed.

Laborit *et al.*^{9,10} studied the effects of the combined K and Mg aspartates on groups of white rats subjected to the standard swim test. It was found that duration of swim after this therapy was significantly prolonged over that achieved with other regimens attempted. After a standard rest period of 2½ hours, the aspartate-treated animals again swam longer than any other group.

Plasma ammonia levels were measured in groups of rats similarly exposed to swim effort and drug therapy. Increase in ammonia levels noted in the controls¹¹ was not seen in the group pretreated with the aspartates.

A group of 16 dogs breathing a mixture of 90% oxygen and 10% CO₂ was given the combined salts of aspartic acid parenterally. Plasma and expired CO₂ tension decreased, and plasma urea concentration increased immediately¹².

The administration of K and Mg aspartates to athletes demonstrated a positive effect on neuro-muscular irritability, a significant reduction in existing fatigue and a significant prophylactic effect against the induction of fatigue^{10,13,14}.

Indications—The use of SPARTASE for the treatment of fatigue is not intended to supplant specific treatment for accompanying organic disease or to substitute for specific indications for potassium.

SPARTASE has a wide range of clinical utility in the management of the fatigue syndrome. It may be used effectively in the management of many fatigue problems, whether or not associated with functional or organic disease. SPARTASE is particularly useful in treating the tired patient with no evidence of organic dysfunction.

Dosage and Administration—The adult dose of SPARTASE is two 500 mg. tablets after the morning and evening meals. Approximately four days therapy are required before subjective clinical improvement may be noted; it is suggested that SPARTASE administration be continued for at least two weeks before the patient is re-evaluated.

Contraindications and Side Effects—Nausea, abdominal discomfort and diarrhea have been noted occasionally. These symptoms may be minimized by proper administration of dose after meals.

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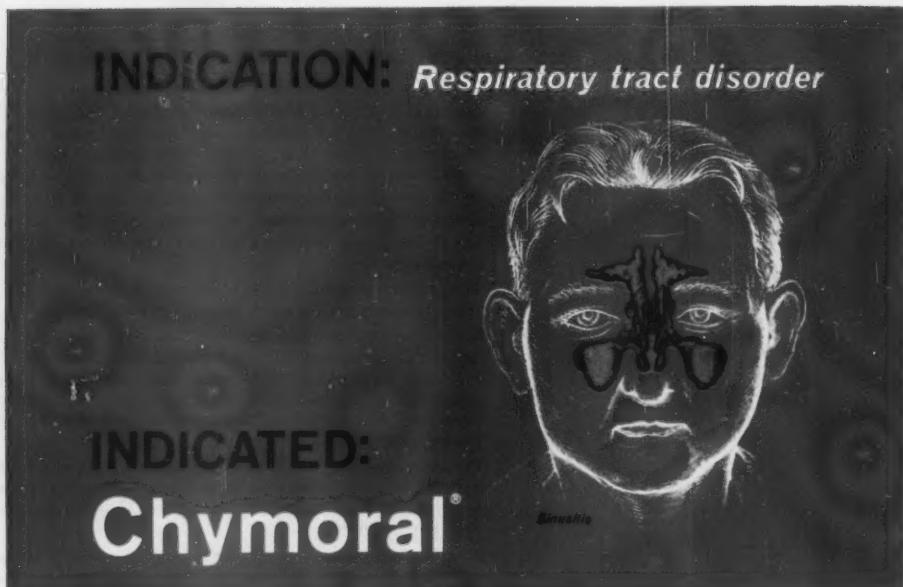
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controls inflammation and edema in respiratory tract disorders¹⁻⁴

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CHYMORAL

Chymoral is an ORAL anti-inflammatory enzyme tablet specifically formulated for intestinal absorption. Each tablet provides enzymatic activity, equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens resolution of blood and lymph extravasations; helps to liquefy thick tenacious mucous secretions; improves regional circulation; promotes healing; reduces pain. INDICATIONS: Chymoral is indicated in respiratory conditions such as asthma, bronchitis, rhinitis, sinusitis; in accidental trauma to speed absorption of hematomas, bruises, and contusions; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapy; in gynecologic conditions such as pelvic inflammatory disease and mastitis; in obstetrics as episiotomies and breast engorgement; in surgical procedures as biopsies, hernia repairs, hemorrhoidectomies, mammectomies, phlebitis and thrombophlebitis; in genitourinary disorders as epididymitis, orchitis and prostatitis; in dental and oral surgery as fractures of the mandible or maxilla, difficult or multiple extractions, and alveolectomies. CONTRAINDICATIONS: None known. INCOMPATIBILITIES: None known. Antibiotics as well as generally accepted measures may be coadministered. SIDE EFFECTS: Mild gastric upsets, rarely encountered. DOSAGE: Recommended initial dose is two tablets q.i.d.; one tablet q.i.d. for maintenance. SUPPLIED: Bottles of 48 and 250 tablets.



ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS • Originators of *Listida*®

CHYMORAL ORAL systemic anti-inflammatory enzyme tablet

Please Mention this Journal when writing to Advertisers

CONTROL BACTERIURIA —WITHOUT PRODUCING RESISTANT MUTANTS

other antibacterials. Mandelamine produces no resistant mutants...is repeatedly effective for recurring infections in the same patient. Prescribe Mandelamine for bacteriuria, symptomatic or asymptomatic...and especially when there is a history of recurring lower urinary tract infections.

Dosage: Adults — Two Mandelamine Hafgrams four times a day. **Precautions:** Mandelamine is contraindicated in patients with renal insufficiency and/or severe hepatitis. An occasional patient may experience gastrointestinal disturbance. **Supplied:** Mandelamine Hafgram® Tablets (0.5 Gm.), and pleasantly flavored Mandelamine Suspension. Mandelamine Sensi-Discs are available from Laboratory Supply Houses. Full dosage information, available on request, should be consulted before initiating therapy.

MANDELAMINE®

brand of methenamine mandelate
the urine-specific antibacterial

MONOGRAM OF
TEGRAL GELUSIL PROLID PERITRATE



MORRIS PLAINS, N.J.



SP17

THERAPEUTIC INDEX

"Thiosulfil" Forte 0.5 Gm. Tablet

BRAND OF SULFAMETHIZOLE

"THIOSULFIL" has been found effective against the following urinary pathogens: *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus fecalis*, *Escherichia intermedium*, and *Aerobacter aerogenes*. In individual cases, sensitivity of the organisms may vary. Sensitivity tests, preferably by the tube dilution method, should be done first, for guidance as to alternate therapy in case "THIOSULFIL" FORTE does not control the infection.

INDICATIONS: Treatment of cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amenable to sulfonamide therapy; prior to and following genitourinary surgery and instrumentation; prophylactically, in patients with indwelling catheters, ureterostomies, urinary stasis, and cord bladders.

SUGGESTED RANGE OF DOSAGE: Adults: 1 or 2 tablets (0.5 Gm.-1.0 Gm.) three or four times daily.

WARNING: Due to the high solubility in body fluids of "THIOSULFIL" and its acetyl form, the hazards of renal tubule obstruction are minimized. The usual precautions exercised with sulfa drugs generally should, however, be observed. In those rare instances where exanthema, urticaria, nausea, emesis, fever or hematuria, are encountered, administration should be discontinued.

CONTRAINDICATION: A history of sulfonamide sensitivity.

SUPPLIED: NO. 788 - "THIOSULFIL" FORTE — Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE — NO. 785: "THIOSULFIL" — Each tablet contains sulfamethizole 0.25 Gm. (scored), in bottles of 100 and 1,000. **No. 914 - "THIOSULFIL" Suspension** — Each 5 cc. (teaspoonful) contains sulfamethizole 0.25 Gm., in bottles of 4 and 16 fluidounces.

SUGGESTED DOSAGES: Adults: 0.5 Gm. four times daily. Infants: (Up to 20 lb.) 25 to 30 mg. per pound per day in four divided doses. Children: (20 to 50 lb.) up to 150 mg. four times daily; (50 to 75 lb.) up to 300 mg. four times daily; (over 75 lb.) adult dose.

WHEN ANALGESIA IS DESIRED

"THIOSULFIL"-A FORTE NO. 783:

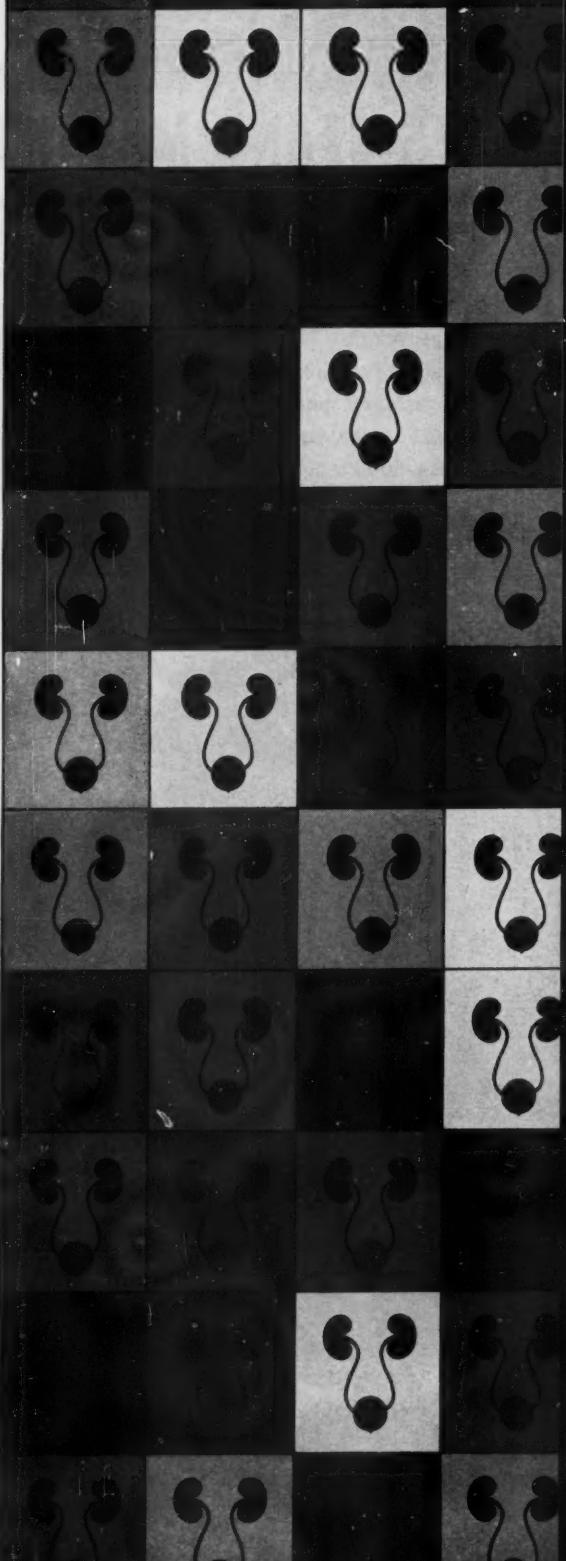
Each tablet contains sulfamethizole 0.5 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

CONTRAINDICATIONS: (1) a history of sulfonamide sensitivity and (2) due to the phenylazo-diamino-pyridine HCl component, renal and hepatic failure, glomerulonephritis, and pyelonephritis of pregnancy with gastrointestinal disturbances.

USUAL DOSAGE: Adults: 2 tablets, four times daily. Children (9 to 12 years): 1 tablet, four times daily.

ALSO AVAILABLE: NO. 784 "THIOSULFIL"-A — Each tablet contains sulfamethizole 0.25 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000. **USUAL DOSAGE:** Adults: 2 tablets, four times daily. Children (9 to 12 years): 1 tablet, four times daily.

For references, see opposite page.



SAFELY MANAGES ALL EPISODES OF URINARY TRACT INFECTION

"Thiosulfil"® Forte 0.5 Gm. Tablet

(BRAND OF SULFAMETHIZOLE)

THE ONE SULFONAMIDE THAT OFFERS

- Maximum urinary concentration of active, free sulfa at site of infection
- Rapid clearance (noncumulative)
- Rare incidence of side effects
- High degree of clinical effectiveness

"Thiosulfil" dosage schedules reported in the literature.

INITIAL EPISODE (Acute Infection) 3 Gm./day¹

Based on 7 years' clinical experience in treating 3,057 cases of upper and lower urinary tract infection, Bourque¹ found 3 Gm./day for 2 weeks (the average dosage employed in 97 per cent of patients) effective in most cases.

RECURRING EPISODE (Flare-up) 3 Gm./day¹

Same dosage as above. When longer therapy is required as in cases where there is stasis due to obstruction, administration may be continued at a lower dosage range.

CONTINUING EPISODE (Stasis/Obstruction) 2 Gm./day^{2,3} 0.5 Gm./day⁴

Where infection remains latent due to causes which cannot be eliminated as in paraplegia, patients have been maintained symptom-free on dosage regimens ranging from 2 Gm. to 0.5 Gm./day. After initial control of acute symptoms, therapy may be continued indefinitely on a low dosage basis to guard against recurrence and prevent ascending infection. Many cases can be controlled with as little as 0.5 Gm./day.



SUPPLIED: No. 786—"Thiosulfil" Forte—Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE—In urinary tract infection—to alleviate pain and control the infection: No. 783—"THIOSULFIL"-A FORTE combines the sulfonamide specific for urinary tract infection with a potent analgesic for prompt, soothing relief of local discomfort. Each tablet contains sulfamethizole 0.5 Gm. and phenylazo-diamino-pyridine HCl 50 mg., in bottles of 100 and 1,000 tablets.

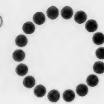
References: 1. Bourque, J.-P., and Gauthier, G.-E.: L'Union Médicale 88:640 (May) 1960. 2. Cottrill, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 58:66 (Mar.) 1959. 3. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. 88:337 (Apr.) 1953. 4. Hughes, J., Copridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

 **Ayerst Laboratories**
New York, N. Y. • Montreal, Canada



IN FUNCTIONAL G.I. AND BILIARY DISTURBANCES ... TO EACH PATIENT ACCORDING TO THE NEED

DECHOLIN-BB®



Hydrocholeretic • Antispasmodic • Sedative...to reduce **TENSION** and anxiety-induced dysfunction of G.I. and biliary tracts...and also relieve both smooth-muscle **spasm** and biliary/intestinal **stasis**

butabarbital sodium	15 mg. (1/4 gr.)
(Warning—may be habit forming)	
dehydrocholic acid, AMES	250 mg. (3 3/4 gr.)
belladonna extract	10 mg. (1/6 gr.)

DECHOLIN® with Belladonna

Hydrocholeretic—Antispasmodic...to relax **SPASM** of smooth muscle of G.I. tract and sphincter of Oddi...and also counteract biliary/intestinal **stasis**

dehydrocholic acid, AMES	250 mg. (3 3/4 gr.)
belladonna extract	10 mg. (1/6 gr.)

DECHOLIN®

Hydrocholeretic...to combat **STASIS** in bowel and biliary tract...by activating biliary function with a greatly increased flow of aqueous "therapeutic" bile

dehydrocholic acid, AMES	250 mg. (3 3/4 gr.)
--------------------------------	---------------------

Average adult dose: 1 or, if necessary, 2 tablets three times daily.

Side effects: DECHOLIN by itself, or as an ingredient, may cause transitory diarrhea. Belladonna in DECHOLIN with Belladonna and DECHOLIN-BB may cause blurred vision and dryness of mouth.

Contraindications: Biliary tract obstruction, acute hepatitis, and (for DECHOLIN with Belladonna and DECHOLIN-BB) glaucoma.

Precautions: Periodically check patients on DECHOLIN with Belladonna and DECHOLIN-BB for increased intraocular pressure. Also observe patients on DECHOLIN-BB for evidence of barbiturate habituation or addiction, and warn drivers against any risk of drowsiness.

Available: DECHOLIN-BB, in bottles of 100 tablets; DECHOLIN with Belladonna and DECHOLIN, in bottles of 100 and 500.

AMES
COMPANY, INC.
Elkhart • Indiana
Toronto • Canada



31161

Butazolidin[®] Geigy

in arthritis and allied disorders

Proved by a decade of experience
Ten years of world-wide experience... almost 2000
published reports... have progressively entrenched
Butazolidin as the leading nonhormonal antiarthritic
agent.

In virtually all forms of arthritic disorder, Butazolidin
affords prompt symptomatic and objective improvement
without development of tolerance... without
danger of hypercortisolism.

Butazolidin[®], brand of phenylbutazone, tablets of
100 mg.; Butazolidin[®] elka capsules containing
Butazolidin, 100 mg., dried aluminum hydroxide gel,
100 mg.; magnesium trisilicate, 150 mg.; homatropine
methylbromide, 1.25 mg.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

SU 564-61

for potential ulcer...

to relieve tensions and to inhibit
hypermotility and hypersecretion

PATHIBAMATE®

PATHILON® tridihexethyl chloride Lederle with meprobamate

highly effective with minimal side effects for therapeutic/prophylactic treatment of duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, gastric hypermotility.

CONTRAINDICATIONS: glaucoma; pyloric obstruction; obstruction of the urinary bladder neck. Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.



for patent ulcer...

to relieve tensions and to inhibit
hypermotility and hypersecretion

PATHIBAMATE®

PATHIBAMATE-400 (full meprobamate effect)—1 tablet t.i.d. at mealtime, and 2 tablets at bedtime • PATHIBAMATE-200 (limited meprobamate effect)—1 or 2 tablets t.i.d. at mealtime, and 2 tablets at bedtime • Adjust to patient response. Each Pathibamate-200 tablet contains: PATHILON, 25 mg.; meprobamate, 200 mg. Pathibamate-400 tablets contain 400 mg. meprobamate. The usual precautions pertaining to the administration of meprobamate should be observed.



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

*Ann Woodward,
Director*

A Man Walked Into Our Office Yesterday



A PHYSICIAN WHOSE EXCEPTIONAL QUALIFICATIONS will certainly win early recognition for him in some fine hospital or with some farsighted group of practitioners.

Training. Experience Age. Working Capacity. Personal adaptability. On all these counts this outstanding candidate's rating is high, and somewhere his abilities are going to be promptly and decisively welcomed.

Possibly he is the man your hospital or your office has sorely needed. If this should be the case, we do indeed covet the satisfaction of presenting his credentials!

OUR 64TH YEAR

WOODWARD
MEDICAL PERSONNEL BUREAU
FORMERLY AZNOES • 185 N. WABASH • CHICAGO

Founders of the counseling service to
the medical profession, serving medicine
with distinction over half a century.



Can we measure the patient's comfort?

Not objectively, as the BMR can be measured by oxygen consumption.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

Alphadrol*

Upjohn
75th year

See page 91 for description, indications, dosage, precautions, side effects, and how supplied.

The Upjohn Company, Kalamazoo, Michigan
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FLUORENDIOLONE, UPJOHN

THE AMERICAN COLLEGE OF PHYSICIANS Schedule of Postgraduate Courses, Fall-Winter, 1960-1961

These courses have been arranged through the generous cooperation of the directors and institutions at which the courses will be given.

Full details may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa. Fees A.C.P. Members, \$60.00, Non-members, \$80.00.

Course No. 4, ADVANCES IN ELECTROCARDIOGRAPHY, New York University Medical Center, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director.

Course No. 5, INTERNAL MEDICINE—TODAY'S PROBLEMS IN DIAGNOSIS AND MANAGEMENT, AND TOMORROW'S PROJECTIONS, Ochsner Foundation Hospital, New Orleans, La.; A Seldon Mann, M.D., F.A.C.P., and William D. Davis, Jr., M.D., F.A.C.P., Co-Directors.

Course No. 6, MEDICAL GENETICS, The University of Michigan Medical School, Ann Arbor, Mich.; James V. Neel, M.D., F.A.C.P., Director.

Course No. 7, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS, Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., F.A.C.P., and Edward H. Reinhard, M.D., F.A.C.P., Co-Directors.

Course No. 8, SYMPOSIA ON CHALLENGING MEDICAL PROBLEMS, Baylor Univ. College of Medicine, Houston, Tex.; Raymond D. Pruitt, M.D., F.A.C.P., Director.

	Dec.		Jan.		Feb.
4-7	4-8				
	11-15	18-22	1-5	15-19	5-9
		25-29	8-12	22-26	12-16
			Jan. 29-Feb. 2		19-23
			15-18		
				29-1	
					X
					X

LIFTS DEPRESSION ...AS IT CALMS ANXIETY

"I feel like my old self again!" Thanks to your balanced Deprol therapy, normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient — they often aggravate anxiety and tension.

And although amphetamine-barbiturate combinations may counteract excessive stimulation — they often deepen depression and emotional fatigue.

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety — a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly — you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly — often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver damage, hypotension or tachycardia.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be increased gradually up to 3 tablets q.i.d. With establishment of relief, the dose may be reduced gradually to maintenance levels.

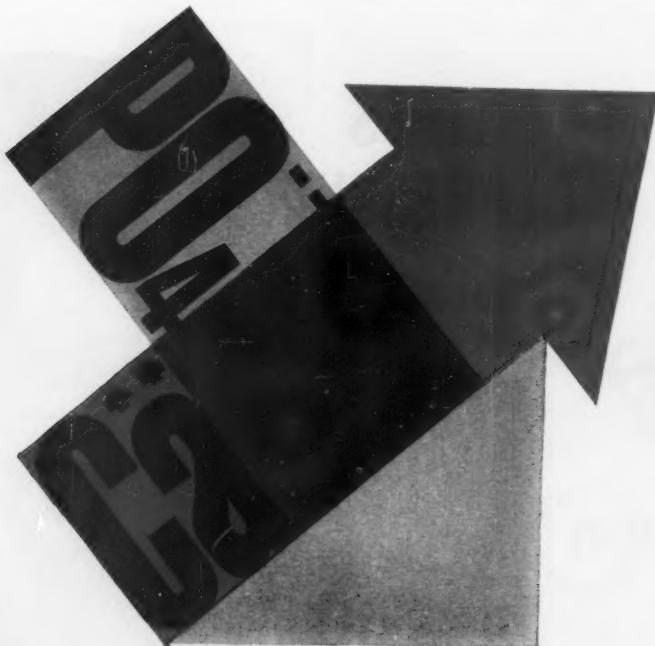
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.



WALLACE LABORATORIES / Cranbury, N.J.

CD-5863



more certain control &
prevention of tetany... **HYTAKEROL**
rapidly restores the normal calcium-phosphorus ratio.

brand of hydrocalciferol

Indications: Hypoparathyroidism (postoperative and idiopathic), pseudohypoparathyroidism, vitamin D-resistant rickets. Prophylactically, following parathyroid surgery, infant diarrhea that may cause tetany, tetany of pregnancy and premenstrual tetany.

Dosage: Treatment must be maintained under careful control of the calcium level of the blood and urine. Initial dose in patients with parathyroid insufficiency, from 3 to 10 ml. (6 to 20 capsules) daily for several days; weekly maintenance dose from 1 to 7 ml. (2 to 14 capsules). Treatment may be supplemented from 10 to 15 Gm. of calcium lactate or gluconate daily, administered orally.

Following thyroid operation, 1 ml. (or 2 capsules) should be given daily with 6 Gm. of calcium lactate orally until the danger of tetany has passed. For the treatment of patients with premenstrual tetany, 1 ml. (or 2 capsules) daily, increased to 1.5 ml. (or 3 capsules) daily, the week before menstruation. To prevent the development of hypocalcemic tetany in infants with severe diarrhea, 1 ml. of Hytakerol should be administered daily with 3 Gm. or more of calcium lactate orally. In patients with vitamin D-resistant rickets, a daily dose of from 1 to 2 ml. (or 2 to 4 capsules) may be given. In patients with pseudohypoparathyroidism, larger than average doses are required; namely, from 3 to 5 ml. (or 6 to 10 capsules) daily.

How Supplied: Hytakerol solution, bottles of 15 ml. Hytakerol capsules (each equivalent to 0.5 ml. Hytakerol solution), bottles of 50. 1 ml. of Hytakerol solution contains the equivalent of 0.25 mg. crystalline dihydrotachysterol.

Winthrop
LABORATORIES
New York 18, N.Y.

Arrest the Coughs that Steal Sleep...

CHRONIC SINUSITIS
PHARYNGITIS
INFLUENZA-COLDS
BRONCHITIS
CHRONIC LUNG DISEASE
CARDIAC DECOMPENSATION
MEASLES



Prescribe

TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

8-12 Hour Cough Control with a Single Dose

- Permits Natural Discharge of Mucus
- Predictable Antitussive Action with Minimum Amount of Narcotic through 'Strasionic' Release

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Rx only. Class B taxable narcotic.

Dose: 1 teaspoonful or tablet q 12 h. Children under 1 year, $\frac{1}{4}$ teaspoonful q 12 h; 1-5 years, $\frac{1}{2}$ teaspoonful q 12 h.

Tussionex—made and marketed only by

STRASENBURGH

In the constant struggle against



EPIDEMIC OBESITY

your patients need your kinds of help

The slender willpower of the obese patient is no match for the heavyweight forces of commercial temptation. Millions of dollars are spent to obsess him with the fattening, forbidden foods that have made obesity "epidemic" . . . while more millions promote the latest fads in diets. No wonder the patient, bedeviled and bewildered, loses the struggle against temptation . . .

For willpower alone is not enough. Your kinds of help are sorely needed. You alone can meet the patient's individual need for authoritative diagnosis and advice in the struggle against overweight. You alone can help the patient deal with underlying emotional factors and establish sensible eating habits.

It can be a difficult task. Temptation sometimes triumphs. But not as often, when your kinds of help include your selective use of . . .

for "sedentary" overeaters

BIPHETAMINE® PHENTERMINE RESIN a 'strasionic' release anoretic

Each capsule of each strength contains equal parts of d-amphetamine and dl-amphetamine as cation exchange resin complex of sulfonated polystyrene. Effects: 10-14 hour appetite appeasement with mild invigoration. Side Effects: When they occur, these may include dryness of mouth, insomnia, and other signs of mild central nervous

stimulation. Accidental overdose may be treated by lavage and sedation. Precaution: Although singularly free from side effects, use with initial care in patients hypersensitive to sympathomimetic compounds in coronary disease, severe hypertension, or cardiac irregularity.

BIPHETAMINE '20'

(20 mg.)

BIPHETAMINE '12½'

(12.5 mg.)

BIPHETAMINE '7½'

(7.5 mg.)

for "active" overeaters

IONAMIN® PHENTERMINE RESIN a 'strasionic' release anoretic

Each capsule of each strength contains phentermine (phenyl-tert-butylamine) as a cation exchange resin complex of sulfonated polystyrene. Effects: 10-14 hour appetite appeasement. Side Effects: When they occur, these may include dryness of mouth, insomnia, and other signs of mild central nervous stim-

ulation. Accidental overdose may be treated by lavage and sedation. Precaution: Although singularly free from side effects, use with initial care in patients hypersensitive to sympathomimetic compounds in coronary disease, severe hypertension or cardiac irregularity.

IONAMIN '30'

(30 mg.)

IONAMIN '15'

(15 mg.)

for "refractory" overeaters

BIPHETAMINE-T® PHENTERMINE RESIN a 'strasionic' release anoretic

Each capsule of each strength contains 40 mg. Tuasole® (2-methyl-3-orthotolyl-quinoxalone) and equal parts of d-amphetamine and dl-amphetamine—all as cation exchange resin complex of sulfonated polystyrene. Effects: 10-14 hour appetite appeasement with mild invigoration and reduction of anxiety. Side Effects: When they

occur, these may include dryness of mouth, insomnia, and other signs of mild central nervous stimulation. Accidental overdose may be treated by lavage, catharsis, and sedation. Precaution: Initiate treatment cautiously in hypertension, cardiac disease and in patients hypersensitive to sympathomimetic agents.

BIPHETAMINE-T '20'

BIPHETAMINE-T '12½'

Single Capsule Daily Dose 10 to 14 hours before retiring

STRASENBURGH



When
ULCER
strikes
or
threatens...

AKALON-T

STRASIONIC, TUAZOLE, NERIOL, METHSCOPOLAMINE, AMINO TUAZOLE & NERIOL

12 HOUR POTENT ANTICHOLINERGIC ACTION WITH A SINGLE CAPSULE DOSE

**'STRASIONIC'
RELEASE
MEANS
SUSTAINED
RELIEF**

AKALON-T '5' 5 mg. Methscopolamine and 20 mg. Tuazole (Brand of 2-methyl-3-orthotolyl-quinazolone) as cation exchange resin complexes of sulfonated polystyrene.

AKALON-T '10' 10 mg. Methscopolamine and 40 mg. Tuazole (Brand of 2-methyl-3-orthotolyl-quinazolone) as cation exchange resin complexes of sulfonated polystyrene.

INDICATIONS: Peptic ulcer, gastroenteritis, painful gastrointestinal spasm, hyperacidity, dyspepsia.

DOSE: One capsule q12h.

EFFECTS: 8-12 hour antisecretory, spasmolytic and gastrointestinal calmative action, with a single dose.

SIDE EFFECTS: In case of overdosage, side effects are those of potent anticholinergics—dry mouth, blurred vision, dizziness, difficulty in voiding, constipation.

PRECAUTION: Use with caution in patients with prostatic hypertrophy, or with a history of urinary tract retention secondary to other anticholinergic drugs.

CONTRAINDICATIONS: Glaucoma, urinary bladder neck obstruction and pyloric obstructions.

STRASENBURGH  **LABORATORIES**
ROCHESTER, NEW YORK, U.S.A.
DIV. WALLACE & TIERNAN INC.

Originators of 'Strasionic' (sustained ionic) Release

I HATE YOU... I HATE EVERYBODY



With effective ataractic agents such as SPARINE, the general practitioner or internist is now able to control acutely psychotic patients presenting the picture of rebellion, anxiety and terror.*

SPARINE is exceptionally well suited for such psychiatric and medical emergencies. It controls central nervous system excitation, allays apprehension and anxiety, calms the agitated patient, stops nausea and vomiting. The prompt effects produced by parenteral SPARINE can be maintained by oral administration.

Wyeth Laboratories Philadelphia 1, Pa.

*Kieve, R.: Am. Practitioner and Digest Treatment 10:965 (June) 1959.

For further information on limitations, administration and prescribing of SPARINE, see descriptive literature or current Direction Circular, available on request.

Sparine®

HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

INJECTION TABLETS SYRUP



helps you relieve anxiety and tension

When exaggerated anxiety and tension disturb your patients, prescribe EQUANIL *L-A* Capsules or EQUANIL to restore equanimity and relax muscle tension.

EQUANIL, in either form, is predictable in action and well tolerated. It has been proved effective in millions of patients and its relative safety in use recorded in hundreds of reports.

EQUANIL *L-A* Capsules and EQUANIL do not cause ataxia, extrapyramidal symptoms, or undue sedation. Normal ability to perform work is undiminished. EQUANIL *L-A* Capsules permit uninterrupted therapy with only twice-a-day dosage.



CLINICAL USE CONFIRMS EFFICACY

The effectiveness of EQUANIL has been documented in hundreds of published studies and proved in millions of patients. The following are abstracts from recent reports that further testify to the usefulness of EQUANIL.

in anxiety and tension

Rickels and associates,¹ in a double-blind, controlled study, compared meprobamate with other drugs in psychoneurotic out-patients exhibiting anxiety, tension and mild depression without evidence of organic disease. Of all drugs used "Therapy with meprobamate always produced the more marked change toward significant improvement and most often showed a significant difference between drug and placebo...."

Meprobamate also helped alleviate insomnia by relaxing tense muscles, freeing pent-up energy and diminishing proprioceptive stimuli, thus allowing natural sleep. Meprobamate was noted to be especially effective in relieving insomnia at night without producing the drowsiness during the day associated with some tranquilizers.

For further information on limitations, administration and prescribing of EQUANIL and EQUANIL L-A Capsules, see descriptive literature or current Direction Circular.

in headache and depression of premenstrual tension

In a recent study,² EQUANIL was used to relieve irritability, depression and headache in premenstrual tension. Therapy was begun nine days prior to date of expected menstruation and continued until menstruation commenced. EQUANIL effected complete or pronounced relief of premenstrual symptoms in over half the patients studied.

in the symptoms of the menopause

Pollak³ in a double-blind trial noted that EQUANIL reduced lethargy and irritability associated with the menopause. The investigator stated: "The troublesome symptoms of undue lethargy and fatigue and the disturbing symptoms of irritability and nervousness were markedly improved by meprobamate [EQUANIL]. . ." EQUANIL also imparted a general feeling of well-being.

References: 1. Rickels, K., et al.: J. Am. Med. Assoc. 171:1649 (Nov. 21) 1959. 2. Appleby, B.P.: Brit. Med. J. 1:391 (Feb. 6) 1960. 3. Pollak, M.: Practitioner 184:231 (Feb.) 1960.

Wyeth Laboratories Philadelphia 1, Pa.



Hypertension
and
heart stress:

Serpasil®
can
control
both!



Serpasil lowers blood pressure gently, guards against cardiac damage

Serpasil—in addition to its well-established effectiveness in controlling high blood pressure—offers an important bonus in treating hypertension. Laboratory studies show that Serpasil can prevent stress-induced heart damage,^{1,2} presumably through its ability to deplete the catecholamines (epinephrine and norepinephrine) from the myocardium.^{3,4}

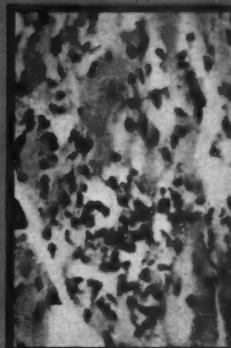
These laboratory data are clinically significant in light of growing evidence⁵⁻⁷ that more than purely "mechanical" overwork may be involved in cardiac damage associated with hypertensive disease. Raab⁵ suggests that much of this damage is due to a direct metabolic action of the catecholamines on heart muscle. The way to prevent it, he believes, is to deplete or inactivate excess catecholamines.

Thus, Serpasil not only eases the mechanical burden on the heart by reducing peripheral resistance and slowing heart rate, it may also provide protection against catecholamine-induced heart damage—the added benefit in prescribing Serpasil for hypertension.

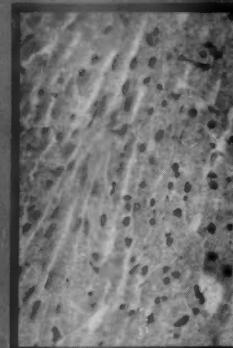
References: 1. Raab, W., Stark, E., and Gigeo, W.R.: Circulation 20:254 (Oct.) 1959. 2. Raab, W.: Research report to CIBA. 3. Carlsson, A., Rosengren, E., Bertler, A., and Nilsson, J.: *Psychotropic Drugs* (edited by Gazzola, S., and Ghetti, V.), Elsevier Publishing Company, Amsterdam, 1957, pp. 268-272. 4. Weud, D.R., Kothiyal, S.R., and Krayer, D.: *J. Pharmacol. & Exper. Therap.* 124:340 (Dec.) 1958. 5. Raab, W.: *Am. J. Cardiol.* 5:371 (May) 1958. 6. Bayer, O., Borden, N.E., Boenninghausen, H., and Eller, S.: *Ztschr. klin. Med.* 148:807 (June) 1958. 7. Raab, W.: *Hormonal and Neurogenic Cardiovascular Disorders*, The Williams & Wilkins Company, Baltimore, 1953, pp. 47, 48.

LABORATORY EVIDENCE SHOWS SERPASIL PREVENTS STRESS-INDUCED HEART DAMAGE*

Severe heart damage in unprotected stressed rat. Tissue taken from rat given 2-a-methyl-8-a-fluorohydrocortisone and stressed (by restraint) for 18 hours. (Photomicrographs from Raab.⁵)



No heart damage in stressor rat protected with Serpasil. Tissue taken from rat given 2-a-methyl-8-a-fluorohydrocortisone and stressed as at left, but also given Serpasil (84 microgram daily for one week).



Note: While Serpasil did not completely protect the hearts of all animals in this study, it greatly reduced myocardial damage in most of them. Original magnification of photomicrographs approximately 450 X.

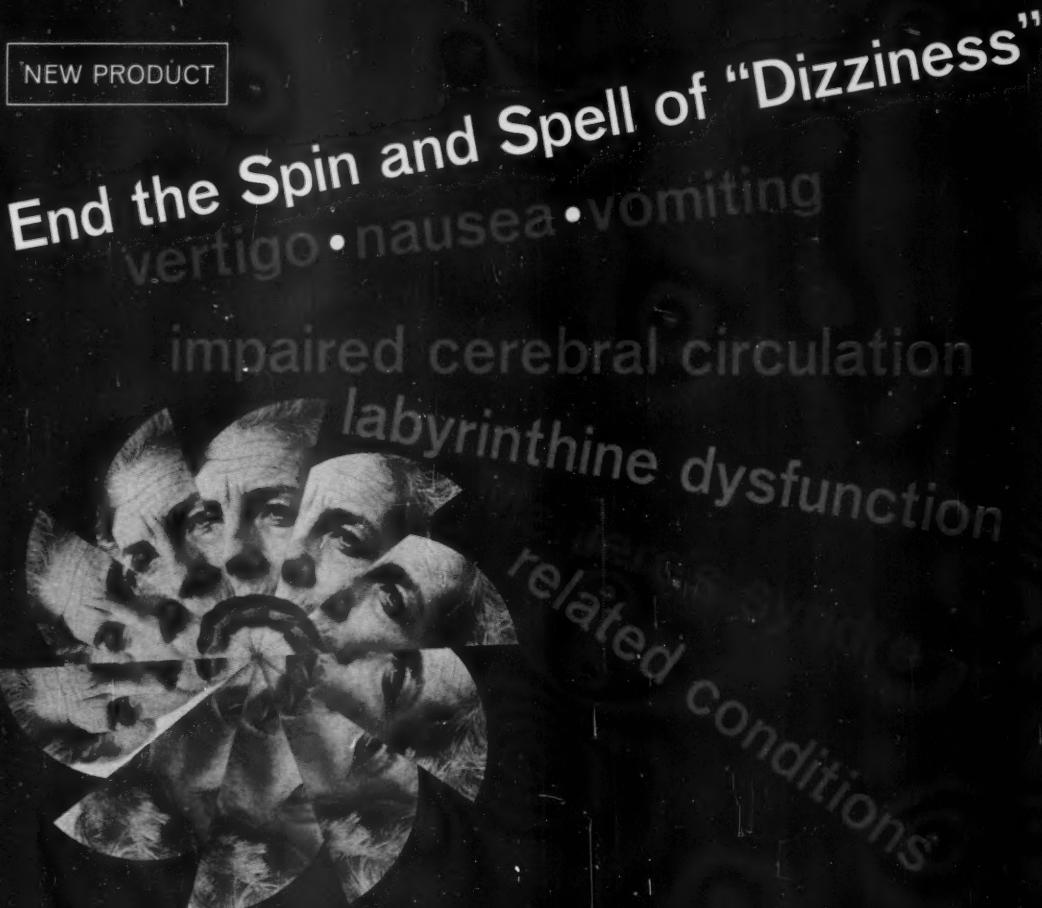
Complete information about indications, dosage, cautions, and side effects of Serpasil—as well as a full report on its heart-protecting action—will be sent on request.

SUPPLY: Tablets, 0.1 mg., 0.25 mg. (scored) and 1 mg. (scored).

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AVAILABLE: Pink capsules, each providing 50 mg Roniacol in the form of the tartrate and 100 mg Tigan HCl, bottles of 50. USUAL ADULT DOSAGE: One or two capsules three times daily. NOTE: Side effects were virtually absent except for a few instances of flushing and an occasional case of skin rash, which disappeared when medication was withdrawn. There are no known contraindications, but as with any new drug, patients should be observed periodically while on Tigacol therapy.

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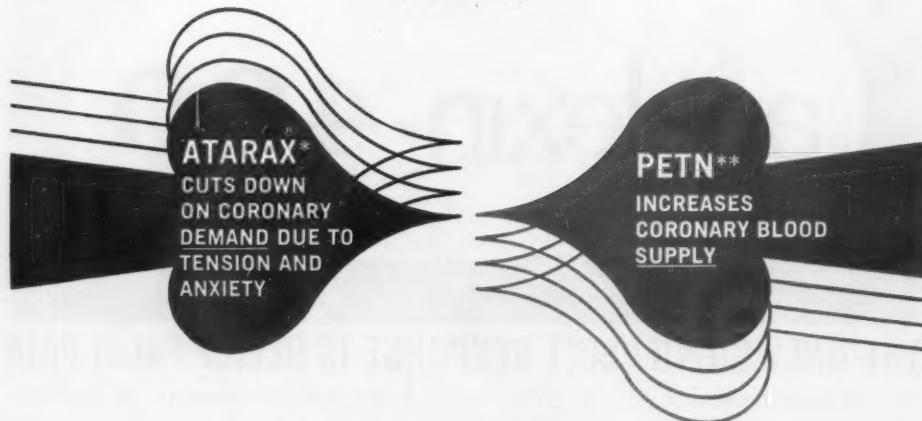
"The practicing physician translating this into his own needs may be completely confident of using a medication with an excellent predictability and a safe analgesic response."¹¹

REFERENCES: From the Symposium, *Recent Concepts of Pain and Analgesics*, held in the Hall of States, American Hospital Association, Chicago, February 15, 1961: 1. Batterman, R. C.: *Non-Narcotic Analgesia in Ambulatory Patients*. 2. O'Dell, T. B.: *Experimental Parameters in the Evaluation of Analgesics*. 3. Miller, L. D.: *Distribution, Excretion and Metabolic Fate of Phenylramidol*. 4. Beisler, E.: *Preliminary Report of Experience with Phenylramidol for Dental Analgesia*. 5. Bader, G.: *Preliminary Report on the Use of Analexin for Dysmenorrhea in Telephone Operators*. 6. Taylor, S. L.: *Phenylramidol in General Hospital Orthopedics*. 7. Bodl, T.: *Pain Management Among Clinic Outpatients*. 8. Ramunis, J.: *Experience of an Industrial Surgeon with Phenylramidol*. 9. Kast, E. C.: *Methodological Considerations in the Clinical Evaluation of an Analgesic*. 10. Collopy, C. T.: *Preliminary Comparisons of Two Non-Narcotic Analgesic Agents in Hospitalized Orthopedic Patients*. 11. Cass, L. J.: *Report on the Analgesic and Calmative Effectiveness of Two Preparations on Patients with Acute and Chronic Pain*. 12. Lamphier, T. A.: *Intravenous Phenylramidol in the Management of Low Back Pain and Allied Disorders*. 13. O'Dell, T. B.: *Chicago Med. 63:203, 1960*. 14. Kast, E. C.: *Chicago Med. 63:17, 1961*. 15. Wainer, A. S.: *J. Am. M. Women's A. 16:218, 1961*. 16. Batterman, R. C.: *Ann. New York Acad. Sc. 86:203, 1960*. 17. O'Dell, T. B.: *Ann. New York Acad. Sc. 86:191, 1960*. 18. O'Dell, T. B., et al.: *J. Pharmacol. & Exper. Therap. 72:85, 1960*. 19. O'Dell, T. B., et al.: *Med. Proc. 18:1694, 1959*. 20. Gray, A. P., et al.: *J. Am. Chem. Soc. 87:4347, 1959*. 21. Wainer, A. S.: *Clin. Med. 7:2331, 1960*. 22. Clinical data in files of Medical Dept., Irwin, Neisler & Co., 1959. 23. Batterman, R. C., et al.: *Am. J. Med. Sc. 238:315, 1959*.

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1. Clark, T. E., and Jochem, G. G.: Angiology 11:361 (Aug.) 1960.

*brand of hydroxyzine **pentaerythritol tetranitrate



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CYTOTOXIC AGENT for palliative chemotherapy
of certain types of malignant neoplasms

Cytoxan demonstrated therapeutic advantage over other agents in a recent 12-month study* of 130 patients, most of whom were refractory to previous treatment:

DISEASE	NUMBER OF PATIENTS	RESULTS				INADEQUATE TRIAL
		GOOD	FAIR	TRANSIENT	FAILURE	
Lymphoma	74	34	3	5	23	9
Hodgkin's Disease	29	10	3	4	9	3
Lymphosarcoma	21	15	0	0	3	3
Multiple Myeloma	16	9	0	0	4	3
Reticulum Cell Disease	8	0	0	1	7	0
Leukemia	23	10	0	0	8	5
Chronic Lymphatic Leukemia	8	4	0	0	3	1
Acute Monoblastic Leukemia	11	5	0	0	3	3
Acute Myeloblastic Leukemia	4	1	0	0	2	1
Carcinoma (Breast, Lung, and Solid Tumors)	29	2	1	1	23	2
Miscellaneous (Mycosis, Fungoides, Psoriasis)	4	0	0	1	3	0
Total	130	46	4	7	57	16

Adapted from Wall, R. L., and Conrad, F. G.

Note that the neoplastic disorders most responsive to Cytoxan were lymphosarcoma, multiple myeloma, Hodgkin's disease, and chronic lymphatic leukemia. Occasionally, good results were observed in acute monocytic leukemia and carcinoma of the breast.

*Other advantages noted in this study**

- multiple routes of administration, permitting prolonged maintenance therapy • lack of latency period for bone marrow depression • failure to produce significant thrombocytopenia • potential therapeutic effect in diseases usually unresponsive to other mustard compounds (e.g., myeloma).

*Wall, R. L., and Conrad, F. G.: Arch. Int. Med. 108:456-482, 1961.

INDICATIONS: Cytoxan is valuable for palliative therapy of certain malignant neoplasms, particularly some of those arising in the reticuloendothelial and hematopoietic systems and certain solid tumors.

Types of cancer which have proved relatively more susceptible or more resistant to Cytoxan therapy may be grouped as follows:

Group I: Neoplasms relatively susceptible to Cytoxan

Hodgkin's disease

Lymphomas: lymphosarcoma; giant follicular lymphoma; reticular cell sarcoma

Leukemia: acute; chronic

Mycosis fungoides

Group II: Neoplasms relatively resistant to Cytoxan

Malignant neoplasms of the breast and the ovary*

Malignant neoplasms of the lung, the gastrointestinal tract and the genitourinary system, including the cervix and the uterus

Malignant neoplasms of miscellaneous origin

Malignant melanomas

*Malignant tumors of these organs are somewhat more susceptible to Cytoxan therapy than are the others included in this group.

DOSAGE: For neoplasms relatively susceptible to Cytoxan

—Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2 to 3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan — Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage — The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient.

Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

ADMINISTRATION: Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

PRECAUTIONS: Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2 to 3 weeks, or debilitated patients.

AVAILABILITY: Cytoxan is available as follows:

Cytoxan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.

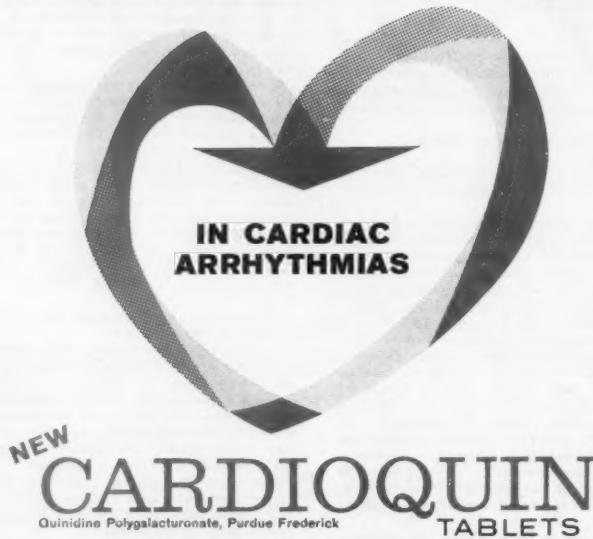


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SUPPLY: Uncoated, scored tablets in bottles of 50.

REFERENCES: 1. Tricot, R., Nogrette, P.: *Presse med.* 68:1085 (June 4) 1960. 2. Schwartz, G.: *Angiology* 10:115 (April) 1959. 3. Shattel, N., Halpern, A.: *Am. J. Med. Sci.* 236:194 (Aug.) 1958. 4. Pote, H. H.: *Angiology* 12:320 (July) 1961. 5. Orgain, E. S.: *Progress in Cardiovasc. Dis.* 2:683 (May) 1960.

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Oral therapy with DIABINESE can help assure more adequate blood-sugar control in many maturity-onset diabetics, including certain patients now poorly controlled by diet alone, some patients on insulin, and many who escape control on previous oral therapy.

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In patients with maturity-onset diabetes whose blood sugar remains elevated despite weight and/or calorie control, DIABINESE is frequently effective in doses of 100 to 250 mg. a day. Further, unlike insulin, DIABINESE has not been reported to increase appetite, and residual capacity for endogenous beta cell activity is stimulated. Thus, DIABINESE combined with dietary regulation will often ensure more satisfactory control than "diet alone."

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DIABINESE has proved to be an effective replacement for insulin among maturity-onset patients needing 40 units or less per day. This application of DIABINESE is especially valuable in patients who should not be exposed to the hazards and inconvenience of self-administered injection—those with poor eyesight, the infirm and elderly, and the emotionally disturbed. Transfer from insulin to DIABINESE in proper dosage lessens the risk of hypoglycemia, and may enable certain patients to resume occupations where insulin shock is considered dangerous.

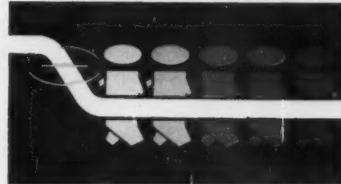
In selected patients in whom insulin requirements have become quite high, combined therapy with DIABINESE sometimes permits reduction of insulin dosage and helps to improve control.³ Patients with insulin resistance may sometimes be similarly helped by replacement of part of the daily insulin dosage.⁴

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Continuous control in suitable candidates for sulfonylurea therapy is more likely to be achieved with DIABINESE. According to the A.M.A. Council on Drugs,⁵ observations indicate that "on an equivalent dose and blood level basis, chlorpropamide has a somewhat greater therapeutic effect than has tolbutamide." This therapeutic superiority is reflected in the results of clinical observations like those of Fineberg,⁶ who compared the effect of DIABINESE in 50 patients with the effect of tolbutamide in 35 patients. He concluded that "chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent)."

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2. El Mahallawy, M. N., and Sabour, M. S.: J.A.M.A. 173:1783, 1960.
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DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are

not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

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Enduron's effect on potassium has upper limits; doubling the single dose from 5 to 10 mg. approximately doubles the output of sodium—yet under this same condition, potassium output increases little or not at all.

Thus Enduron produces less potassium excretion per unit of sodium excreted, so that depletion rarely becomes a problem.

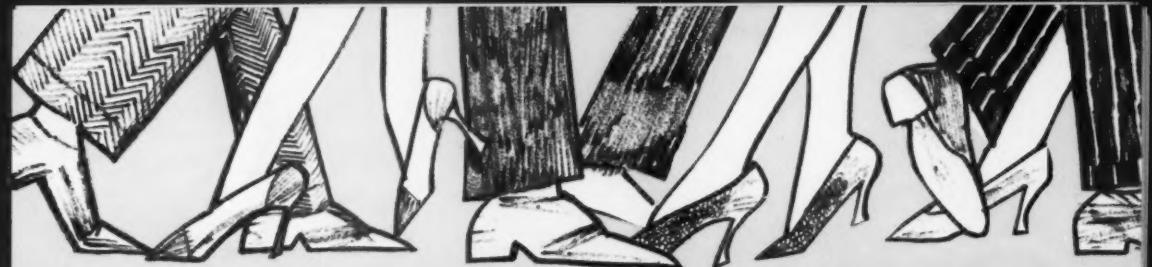
Use Enduron with patients who have mild to moderate hypertension, or patients with edema (as in congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, or steroid therapy). Observe its convenience and effectiveness. *We predict you'll be glad you used it.*



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*Hold down that
soaring blood pressure with
just one daily dose*

NEW THIAZIDE RAUWOLFIA ANTIHYPERTENSIVE

ENDURONYL

(Methyclothiazide and Deserpidine, Abbott)—ENDURON™ and HARMONYL®

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Of course, Enduronyl can't *cure* your patients' hypertension...but it certainly can simplify treatment. It enables you to provide the fullest advantages of thiazide and rauwolfa—in a single convenient agent—and you'll need just *one* dose daily. Note these two components:

1. ENDURON (*Methyclothiazide*)

This long-acting diuretic produces enhanced sodium excretion per unit of potassium excreted and minimal potassium loss. It has amply demonstrated its merit as a primary measure in controlling mild to moderate hypertension.

2. HARMONYL (*Deserpidine*) This is Abbott's distinctive rauwolfa alkaloid. It provides antihypertensive and tranquilizing actions equal to those of reserpine, but with less interference from certain bothersome side effects such as lethargy.

Together, these two components provide even greater antihypertensive action than with either alone. Blood pressure starts down steadily, and improvement should be substantial within 10 days. Use Enduronyl and see. Full literature available promptly on request: contact Abbott Laboratories, North Chicago, Illinois.



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Helps you take the misery out of menopause *as hormones alone often don't do*



Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Milltown alone can sustain the patient.

Composition: Milltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Milltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Milltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

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This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

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and edema****17 days free each month
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Mon. Wed. Fri.**

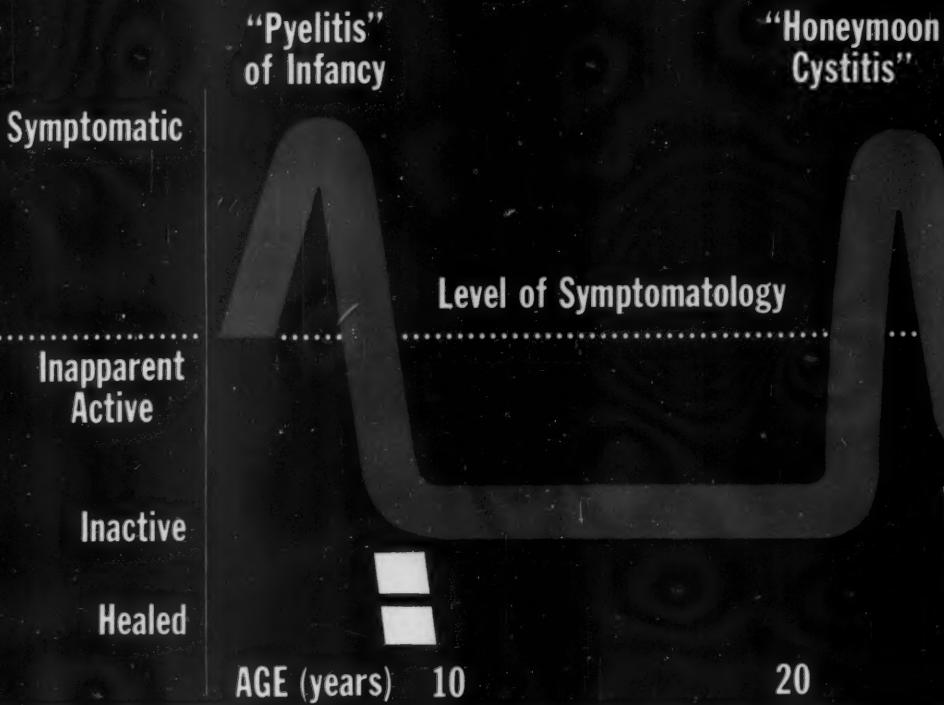
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Natural History of Pyelonephritis



66

"...the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."¹

99

at every age of life...at every stage of infection

Urinary tract infections of childhood are frequent, persistent and difficult to cure. If inadequately treated, serious sequelae in later life are too often the result. **The child-bearing age** represents a second major stage for urinary tract infection, a hazard to both mother and fetus, and a potential precursor of renal insufficiency if not thoroughly eradicated. **During the middle and later years** relapse and reinfection, with the spectre of renal failure, make management a grave problem—preserving function and prolonging life become the realistic therapeutic goals.

"Pyelitis" of
Pregnancy

Pyelonephritis

Asymptomatic
Bacteriuria

Uremia
Hypertension
LV Failure

30

40

50

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control of infection throughout the urinary system**

"... seems to be by far the most effective drug to be employed, and this has been substantiated in practice. It is a drug of low toxicity and, what is more important, bacteria rarely if ever become resistant to it. It can be employed for long periods of time, is bactericidal and does not favor the appearance of monilial infections." 2

Average FURADANTIN Adult Dosage: 100 mg. tablet q.i.d. with meals and with food or milk on retiring. For acute, uncomplicated infections, 50 mg. may be administered. If improvement does not occur in 2 or 3 days, increase the dose to 100 mg. q.i.d. Supplied: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

1. Birchall, R.: Am. Practit. 11:918, 1960. 2. Sanjurjo, L. A.: Med. Clin. N. Amer. 43:1601, 1959.

Complete information in package insert or on request to the Medical Director.

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ARAMINE is always ready for immediate use—no dilution needed.

ARAMINE is also valuable in shock accompanying anaphylaxis, brain damage, infectious disease, hemorrhage, surgery, trauma.

Supplied: In 1-cc. ampuls and 10-cc. vials (10 mg. metaraminol present as the bitartrate per cc.).
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Additional information is available to physicians on request.

1. Selzer, A., and Ryland, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 180:762, (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.



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We recommend that fresh tubing be used for each PERIDIAL® infusion in peritoneal dialysis: a simple precaution to minimize the risk of peritonitis. It would be only a small violation of the principle of the closed system to use the same piece of plastic tubing for an entire series of exchanges, and the patient might be "saved" a few dollars, over the course of a long dialysis.

But this procedure is not recommended. According to Maxwell,* freedom from the threat of peritonitis is largely dependent upon maintenance of an essen-

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*Maxwell, M.H., et al.: JAMA 170:917 (June 20) 1959.

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all day...all night
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after 3 years' clinical experience: here is what we now know about MER/29 and...

WHAT DO WE KNOW ABOUT THE MER/29 EFFECTS

We know that MER/29 lowers cholesterol in 8 out of 10 patients, even without dietary restrictions. In 576 patients studied by various physicians, average cholesterol levels dropped from 303 mg. % to 241 mg. % — an average decrease of 62 mg. %.

We know that MER/29 reduces total sterols in both blood and tissue.

We know that MER/29 does this by inhibiting the body's own production of cholesterol.

We know that its use in over 300,000 patients re-affirms the safety margins established in early laboratory and clinical data.

WHAT DO WE KNOW ABOUT THE MER/29 CARDIOVASCULAR BENEFITS

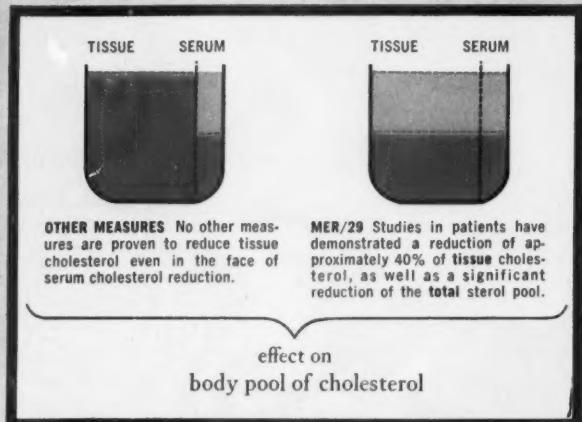
We know that, in some patients, concurrent clinical benefits attend the use of MER/29. Published papers on MER/29 therapy to date report improvement in 50 of the 79 anginal patients reported in these studies, and comparable results are being obtained in similar studies now in progress. Among the other benefits reported are:

**decreased incidence and severity
of anginal attacks**

improved ECG patterns

diminished nitroglycerin dependence

increased sense of well-being



"During triparanol [MER/29] therapy there was a definite improvement in the electrocardiographic tracings in response to exercise in 3 of 11 subjects with angina pectoris."

—Hollander, W., et al.: *J.A.M.A.* 174:5 (Sept. 3) 1960.

"Nitroglycerin requirements decreased in 3 [of 5 out-patient] patients, including the patient showing electrocardiographic improvement....Three [of 4 private male patients], after a lapse of some weeks, showed improvement in exercise electrocardiograms, which was sustained but not further improved in subsequent observations."

—Corcoran, A. C., et al.: *Progr. Cardiovasc. Dis.* 2:(Pt. I) 576 (May) 1960.

"Of the 45 patients with coronary artery disease followed for 1 year, 16 had a history of frequent anginal attacks. Fourteen of these spontaneously stated that their angina disappeared within 2 months of [MER/29] therapy....In one patient...with persistent coronary insufficiency pattern (ST segment depressions in multiple leads), there was a complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in angina."

—Lisan, P.: *Progr. Cardiovasc. Dis.* 2:(Pt. I) 618 (May) 1960.

....what we are learning about atherosclerosis

WHY MER/29 MAY FAVORABLY ALTER ATHEROSCLEROSIS

"It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis."

—Page, I. H.: *Mod. Med.* 29:71 (Mar. 20) 1961.

Epidemiologic studies show that low cholesterol levels are associated with low incidence of atherosclerosis and coronary artery disease.

On the basis of such studies, Stamler has said: "...a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men."

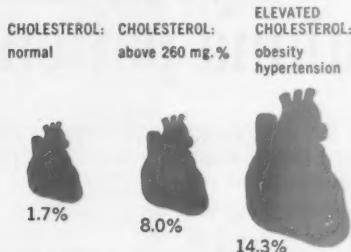
—Stamler, J.: *Am. J. Pub. Health* 50:(Pt. 2) 14 (Mar.) 1960.

THE DECISION FACING THE PHYSICIAN

Despite our knowledge of the action, benefits and safety of MER/29, much remains to be discovered about the basic concept of cholesterol-lowering therapy. In this, MER/29 is comparable to the well-accepted use of anti-hypertensive agents: we know they lower blood pressure, but we cannot prove that lowering blood pressure will also lower morbidity or mortality. Yet few physicians hesitate to use these agents. The possible good is too great to ignore.

So it is with MER/29. No one can yet be certain that sustained lowering of total body sterols

INCIDENCE OF ATHEROSCLEROTIC HEART DISEASE (males, aged 45-62)



—Adapted from Katz, L. N., and Pick, R.: *Heart Bull.* 8:82 (Sept.-Oct.) 1959.

will prevent or alter atherosclerosis. But the current evidence strongly supports this concept.

Perhaps that is why an increasing number of physicians are now prescribing MER/29. They wish to assure their hypercholesterolemic, coronary artery disease, and atherosclerotic patients this reasonable hope.

It is a decision facing every physician.

Complete
bibliography
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on request.



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MER/29

(triparanol)

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BECAUSE VAPONEFRIN HAS SUCH AN OUTSTANDING RECORD OF SUCCESS WITH INTRACTABLE ASTHMA AND EMPHYSEMA PATIENTS, WE MAKE THIS UNUSUAL OFFER...

Free a Vaponefrin® Inhalation Set for your difficult-to-manage asthma patient!

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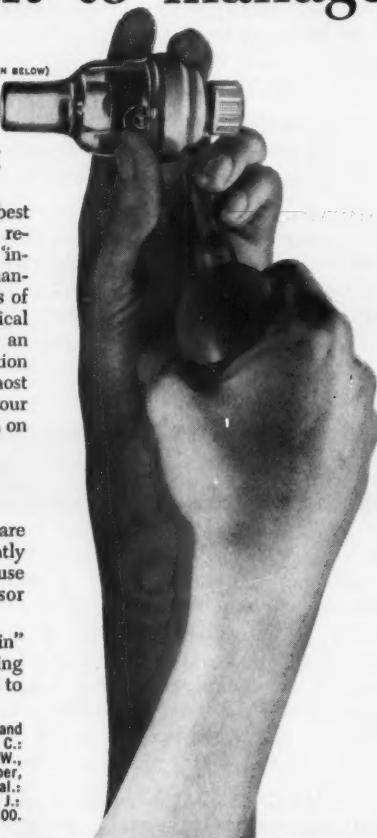
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SUPPLIED: Solution, bottles of 7.5, 15 and 30 cc.; Nebulizers, Standard and Pocket size. Also Aerosol Unit. **REFERENCES:** 1. Digilio, V. A., and Munch, J. C.: Ann. Allergy 13:257, 1955. 2. Bickerman, H. A., and Barach, A. L., in Modell, W., Ed.: Drugs of Choice, St. Louis, The C. V. Mosby Co., 1958-59, p. 582. 3. Farber, S. M., and Wilson, R. H. L.: Ann. Int. Med. 50:1241, 1959. 4. Munch, J. C., et al.: J. Am. Pharm. A. (Scient. Ed.) 40:526, 1951. 5. Segal, M. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema, New York, Grune & Stratton, 1953, pp. 99-100.

*Bibliography available on request.



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 The higher level of relief
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Alphadrol*

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 75th year

See page 91 for description,
 indications, dosage, precautions,
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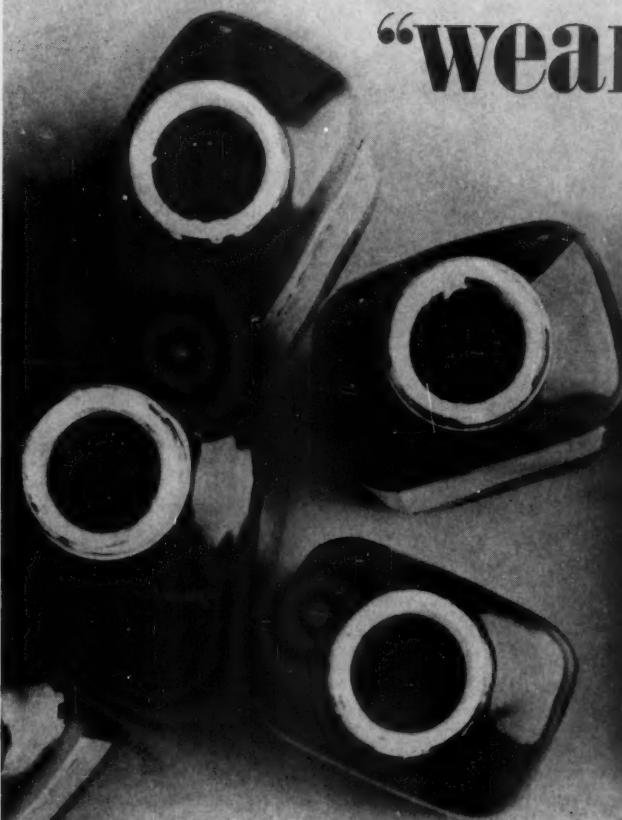
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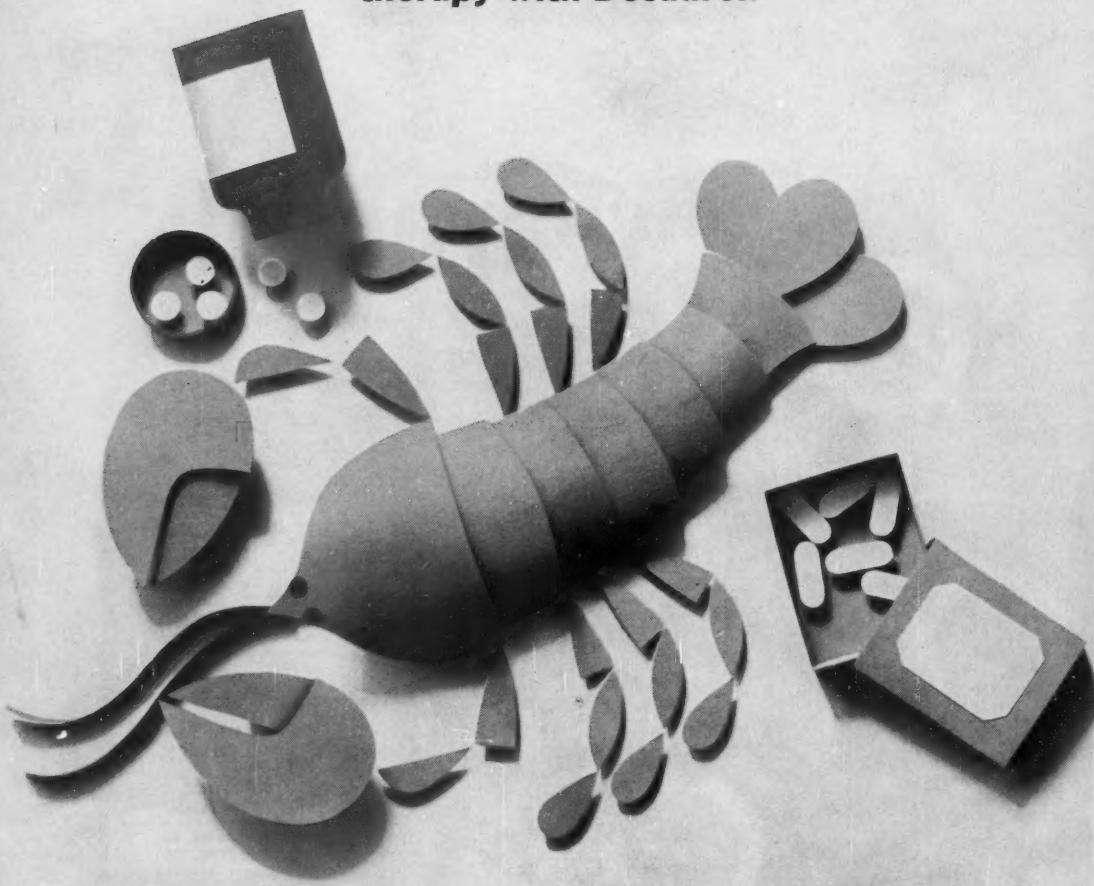
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References: 1. Grater, W. C.: Southern M. J. 53:1144, 1960. 2. Feinberg, S. M.: Med. Sci. Q. (No. 3) 101, 1959.

Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100 and 1000. As Injection DECADRON Phosphate in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21-phosphate as the disodium salt; inactive ingredients: 8 mg. creatinine, 10 mg. sodium citrate; sodium hydroxide to pH 7.8, and water for injection q. s. 1 cc.; preservatives: 0.32 per cent sodium bisulfite and 0.5 per cent phenol. DECADRON is a trademark of Merck & Co., Inc.

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time	amount	administration
1st day	one to two cc. (4 to 8 mg.) Injection DECADRON Phosphate intramuscular	repeated as necessary (In substituting tablet therapy, give the first oral dose four or five hours before the final parenteral dose.)
2nd day	two 0.75 mg. Tablets DECADRON	b.i.d.
3rd day	two 0.75 mg. Tablets DECADRON	b.i.d.
4th day	one 0.75 mg. Tablet DECADRON	b.i.d.
5th day	one 0.75 mg. Tablet DECADRON	per day
6th day	one 0.75 mg. Tablet DECADRON	per day
7th day	RETURN VISIT	



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- Side effects with NACTISOL therapy have been minimal.³⁻⁵

NACTISOL*...in scored, yellow tablets



References

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2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, *Postgrad. Med.* 26:502-509 (October) 1959.
3. Steigmann, F.: Clinical Report to McNeil Laboratories.
4. Lorber, S. H.: Clinical Report to McNeil Laboratories, December 6, 1960.
5. Rider, J. A.: Clinical Report to McNeil Laboratories.

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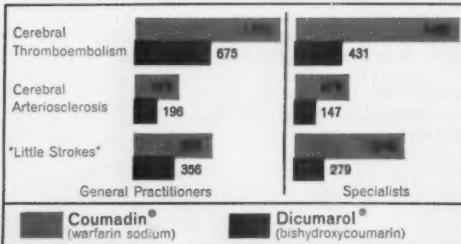
Nationwide Survey Explores Current Use of Anticoagulants in Cerebrovascular Disease

It has been estimated that there are 2,000,000 people suffering from vascular disease of the brain in the United States,¹ and that each year at least 500,000

persons are incapacitated by some kind of cerebral accident.² With the advancing age of our population, this problem is likely to increase.

As reported in previous numbers of this series, Endo Laboratories received replies to its comprehensive *Anticoagulant Survey* from a total of 10,016 physicians across the nation. Among the questions asked were—Are you now using oral anticoagulants for cerebral thromboembolism, cerebral arteriosclerosis, or “little strokes”—therapeutically, prophylactically? Without regard to the anticoagulant chosen, 14.4% of physicians reported use of oral anticoagulation in therapy of cerebral arteriosclerosis, 27.9% in little strokes, and 46.9% in cerebral thromboembolism. Anticoagulation was used prophylactically as follows: 10% in cerebral arteriosclerosis, 16.8% in little strokes, and 21.2% in cerebral thromboembolism.

Comparison of usage was also made among the 61.4% of reporting physicians prescribing Coumadin® most often and the 27.6% using Dicumarol®. (The remainder used indandiones [1.9%] and other anticoagulants.) The following graph shows the application of the leading anticoagulants therapeutically in cerebrovascular disease:



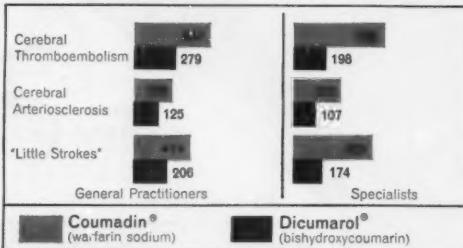
Physicians Using Oral Anticoagulation Therapeutically in Cerebrovascular Disease

Specialists Lead in Therapeutic Application of Anticoagulants

The analysis of the data presented in this survey indicates that 57% of the cardiologists and internists prescribing Coumadin—the most frequently prescribed oral anticoagulant—and 42% of the general practitioners used the drug therapeutically in cerebral thromboembolic disease. It is also noteworthy that 39% of the specialists used Coumadin in therapy of “little strokes” as compared with 22% of the

general practitioners. Less frequent was its use as part of the therapy of cerebral arteriosclerosis—18% among the specialists and 12% among the general practitioners.

Anticoagulation was used less often for prophylaxis than for therapy of cerebral thromboembolism, little strokes, or cerebral arteriosclerosis, as shown in the following graph:



Physicians Using Oral Anticoagulation Prophylactically in Cerebrovascular Disease

Indications According to Recent Clinical Reports

Clinical experience emphasizes the need for careful diagnosis and patient selection before using anticoagulants in cerebrovascular disorders. Authorities are generally agreed that anticoagulants help to minimize the occurrence of attacks in patients with *transient ischemic episodes*,³⁻⁶ which are “far more common than was previously suspected.”⁷ In addition, anticoagulation is advocated in the slowly evolving *stroke*,⁵⁻⁷ i.e., “slow-onset” infarction. Evidence in cases of *cerebral embolism* indicates that anticoagulants may reduce the mortality rate. In patients with *completed cerebral infarction*, the findings of Thomas⁸ indicate that long-term anticoagulant therapy may be valuable in minimizing recurrences and mortality rate. His results also suggest that “there is no time when it becomes safe to discontinue anticoagulant therapy.”⁸ Since the source of cerebral dysfunction may lie in occlusive disease of the carotid arteries in the neck, cerebral angiography is recommended as a valuable means of establishing the diagnosis.^{1,2}

Physicians choosing Coumadin for anticoagulation have reportedly done so (see No. 1 of this series) because of its predictable effect, ease of maintenance, and single daily dose which permit a smoother, more convenient, and less hazardous anticoagulant regimen.

1. Meyer, J. S.: Am. J. Med. 30:577, 1961.
2. Kuhn, R. A.: Current M. Digest 28:51, 1961.
3. Groch, S. N., and Wright, I. S.: Circulation 23:458, 1961.
4. Siekert, R. G.; Millikan, C. H., and Whisnant, J. P.: J.A.M.A. 176:19, 1961.
5. Carter, A. B.: Neurology 11:601, 1961.
6. Marshall, J.: Ibid. 11:139, 1961.
7. Groch, S. N.: Ibid., p. 141.
8. Thomas, A. B.: Minnesota Med. 42:1587, 1959.

Coumadin (warfarin sodium) is manufactured under license from the Wisconsin Alumni Research Foundation, and is supplied as scored tablets of 2 mg., lavender; 2½ mg., orange; 5 mg., peach; 7½ mg., yellow; 10 mg., white; and 25 mg., red, as well as in 50 mg. and 75 mg. single-injection units.



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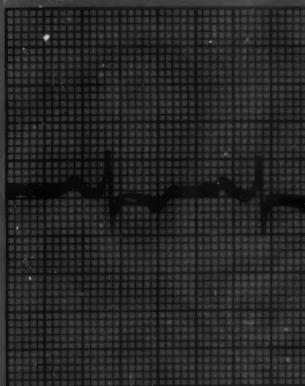
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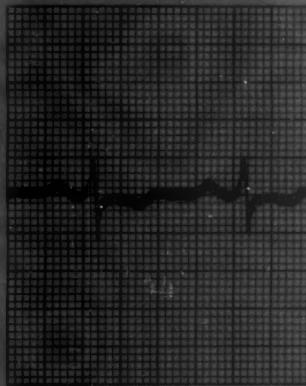
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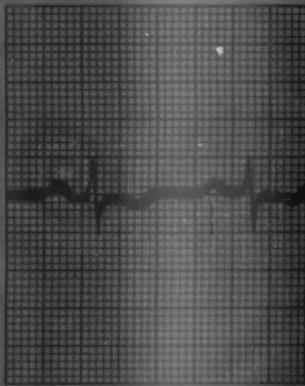
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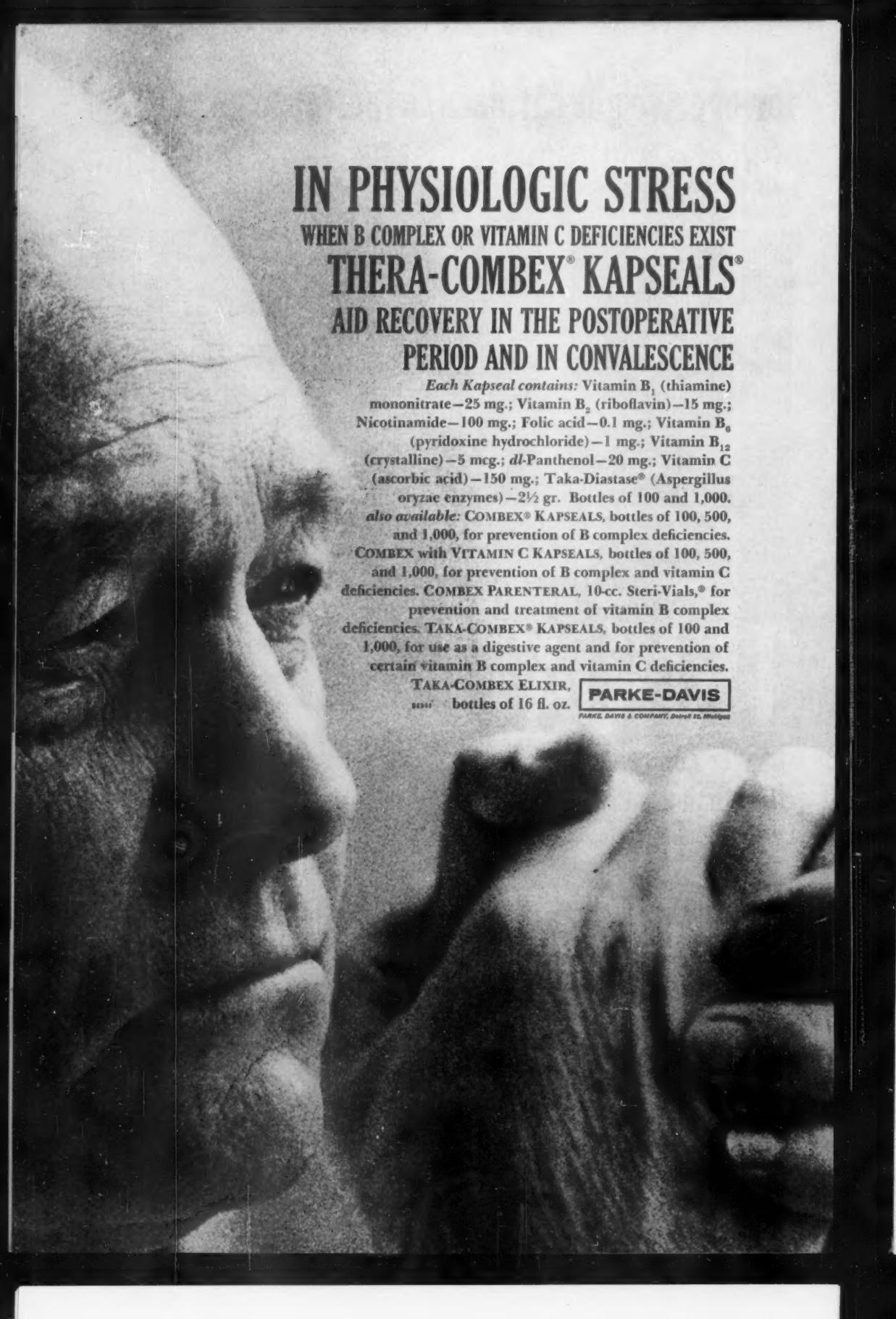
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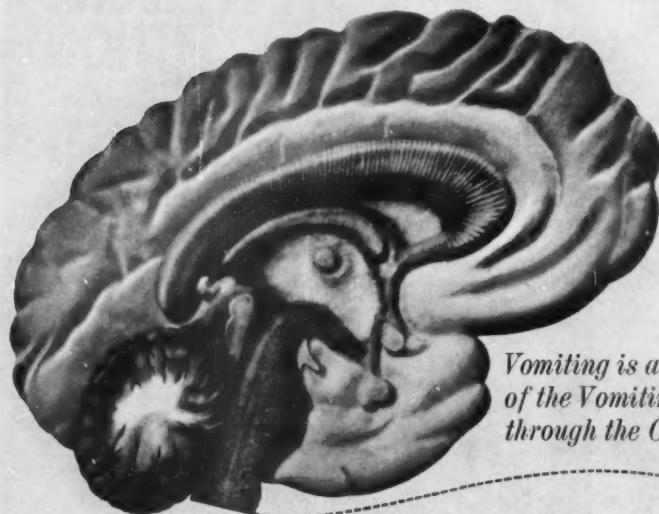
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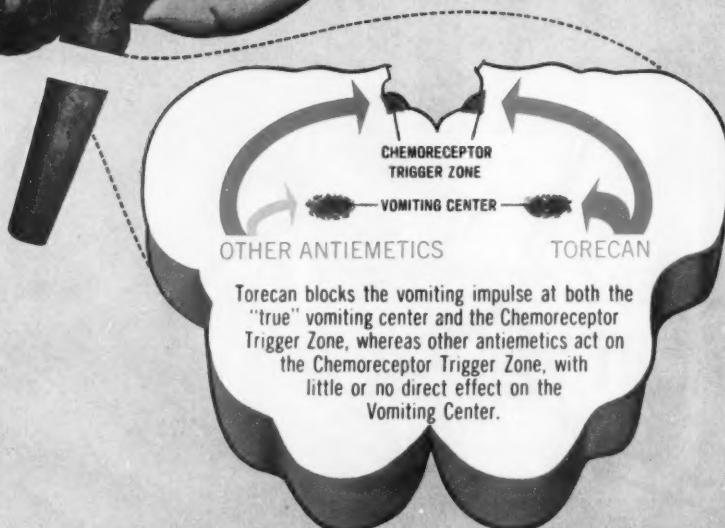


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References: 1. Codiga, V. A.: A new antiemetic for the treatment of nausea and vomiting associated with roentgen therapy, Int. Rec. Med., 174:375 (June) 1961. 2. Wang, S. C. and Borison, H. L.: The vomiting center: Its destruction by radon implantation in dog medulla oblongata, Am. J. Physiol. 166:712 (1951). 3. Wang, S. C. and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides, Gastroenterol. 22:1 (1952). 4. Wang, S. C. and Glaviano, V. V.: Locus of emetic action of morphine and hydazine in dogs, J. Pharmacol. & Exper. Therap. 111:329 (1954). 5. Browne, D. C. and Sparks, R.: Vomiting mechanisms: a clinical study of thiethylperazine, South. M.J., 54:(Sept.) 1961. 6. Browne, D. C. and Sparks, R. D.: Nausea and vomiting, study of thiethylperazine, Scientific Exhibit, American Medical Association Clinical Meeting, Washington, D.C., Nov. 28 (1960). 7. Martino, M., Guerreri, S., Menesini, R.: Prophylaxis and therapy of vomiting, Minerva anest. 26:343 (1960). 8. Modell, W.: Drugs of choice 1960-1961, C. V. Mosby Co., St. Louis, 1960, p. 339.



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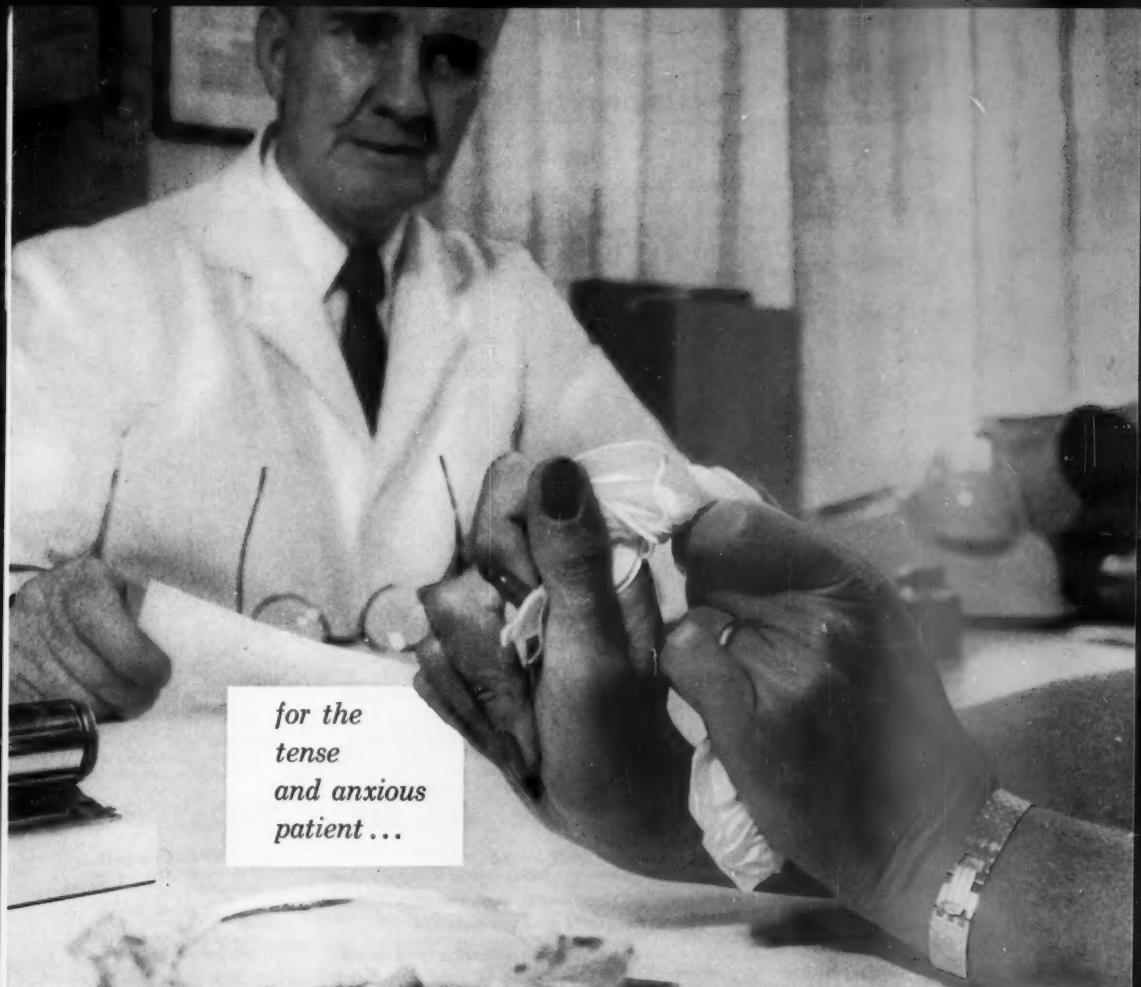
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1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:129, 1960.

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